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Ballistocardiography

II. The Normal Ballistocardiogram

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In this study, the normal ballistocardiogram is interrelated with various cardiac events in order to establish the origin of its component waves. It is apparent that the ballistic F, G, H, I, J, K, L, M and N waves bear a definite relationship to known cardiac events, although in some cases the temporal positioning of the complexes is shifted by uncontrollable forms of distortion. When calculated correction factors are introduced, the ballistic waves tend to assume their correct temporal relationship. A composite pictorial sketch is presented which shows the temporal relationships of the phonocardiogram, the apex cardiogram, two commonly observed forms of the normal ballistocardiogram, the electrocardiogram, and the carotid pulse.

IN ORDER to establish the origin of the component waves which comprise the ballistocardiogram, it is essential to interrelate the ballistocardiogram with simultaneously registered physiologic events which result from cardiac activity. To date, most investigators have been content with merely establishing the identity of a representative ballistic wave such as the H and then calling the subsequent waves by the usual J, K, L, M, N and O terminology. When such procedure is used, a simultaneously registered electrocardiogram is generally adequate as its R wave occurs approximately prior to the ballistic H wave. The carotid pulse has also been used for establishing such relationship as it has been considered a fair indicator of the onset of mechanical systole. The possibilities of the phonocardiogram as a timing reference were suggested by Starr and his associates[1] in 1939 and more recently by Gubner.[2] Jones and Goulder[3] recently stated that their limited experience with the phonocardiogram as a reference tracing indicates that it is a more reliable measure of the onset of mechanical systole. DeLalla[4] observed that the ballistic H wave is nearly synchronous with the first heart sound. Nowhere in the literature is there any evidence to indicate that anyone has taken full advantage of the phonocardiogram as a means for timing the mechanical events in systole and diastole as related to ballistic activity.

Messer and co-workers[5] have shown that the phonocardiogram is a more accurate reference tracing than the electrocardiogram for the exact timing of the beginning of mechanical systole and diastole. Others[6–12] have noted that inaccuracies occur in the determination of the exact onset of mechanical systole by the use of the carotid surface pulse. Although the electrocardiographic R wave is helpful as a rough reference for indicating the beginning of mechanical systole, comparative measurements indicate that the carotid pulse is more reliable than the electrocardiographic R wave but less precise than the phonocardiogram.

The beginning of mechanical systole is indicated in the carotid pulse wave by the rapid or primary deflection which represents the beginning of the rapid ejection of blood into the aorta. Factors such as the amount of pressure which is applied to the artery and the

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method of sensing[7, 13] may affect the indicated time of the initial rapid rise in the graph in the form of a delayed onset; the transmission time of the pulse must also be taken into consideration.

Methods and Material

In this investigation, we employed as reference tracings the phonocardiogram, the various peripheral pulses, the apex cardiogram and the electrocardiogram. The subjects investigated consisted of a group of clinically normal men between the ages of 23 and 47 years. Individual body types varied from ectomorphic to endomorphic, but no extremes of any type were present. The professional staff, postgraduate and medical students in the hospital comprised this group. No athletes in training were included and all subjects were in excellent health.

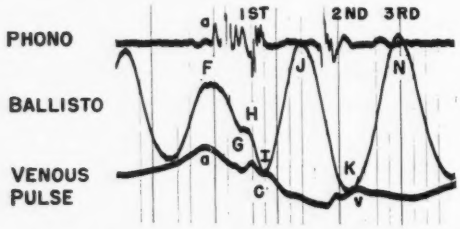

Fig. 1. Simultaneously registered phonocardiogram, ballistocardiogram and venous pulse. The ballistic F wave registers simultaneously with the auricular waves in the phonocardiogram and the venous pulse. Camera speed, 75 mm. per second.

The normal control tracings were obtained at any hour of the day, including in some instances the immediate postprandial period. The type of ballistocardiograph used, its characteristics and the ballistocardiographic technics employed have been discussed in part I of this paper.

The ballistocardiograms were first analyzed with regard to the events represented in the phonocardiogram, the electrocardiogram, the apex cardiogram, the carotid pulse, radial pulse, femoral pulse, jugular pulse, liver pulsations, epigastric pulsations and the aortogram. We observed that the radial pulse, the liver pulsations and the epigastric pulsations were of little value in evaluating the ballistocardiographic complexes and their registrations were subsequently discontinued. The venous pulse which was taken over the internal jugular bulb is difficult to register consistently when the subject is in a supine position such as is required for ballistocardiography. The limited number of satisfactory venous pulse tracings which were obtained did show a constant and finite relationship to the ballistocardiogram. These registrations were helpful when satisfactorily recorded.

Observations

*F Wave.** A wave which we shall call the F wave was found to be present in the majority of ballistocardiograms. This wave is a positive deflection of varying magnitude which occurs before the ballistic G wave[3] and may be seen in figure 1. If the cardiac rate is rapid, it may be lost in the preceding complex. In the normal subject the F wave occurs simultaneously with the auricular sound in the phonocardiogram, between the electrocardiographic P and Q waves, and coincides with the auricular wave of the apex cardiogram. When a satisfactory venous pulse was registered, its *a* wave also coincided with the ballistic F wave. From these observations it is suggested that the ballistic F wave may be of auricular origin.

G Wave. This is a negative deflection, observed by DeLalla, which precedes the ballistic H wave. Our observations also show the presence of a G wave and our records show that it is related to the third component of the first heart sound[13, 14] which is the opening of the semilunar valves and the beginning of mechanical ventricular systole (fig. 2). Our records also show that the second positive peak of the apex cardiogram which denotes semilunar valve activity (fig. 3), as well as the onset of the surface carotid pulsation, coincide with the G wave (fig. 4). The onset of the *c* wave of the venous pulse coincides with the ballistic G wave.

H Wave. This wave appears to occur simultaneously with the fourth component of the first heart sound[13, 14] which is best registered on the stethoscopic phonocardiograms[15] (fig. 2). The ballistic H wave also coincides with the second negative deflection, on the descending slope of the negative wave or the rise of the systolic plateau in the period denoted as systole in the apex cardiogram (fig. 3). Some temporal variations have been observed in this respect which may be due to phase shift effects upon the ballistocardiographic complexes described in part I of this paper.

The fourth component of the first heart

* Since the completion of this paper, a reference to this wave has been made by Luisada, A. A. and Contro, S.: On the time relationship of the waves of the ballistocardiogram, Acta Cardiologica, **5**: 847 1951.

sound[13, 14] has been ascribed to the acceleration of blood in the great arterial vessels during the ejection phase of ventricular systole. The above observation, together with that concerning the ballistic I wave, offers an alternate possible cause of the fourth component of the first heart sound and will be discussed in a later communication. The apex of the venous pulse *c* wave appears to occur simultaneously with the ballistic H wave.

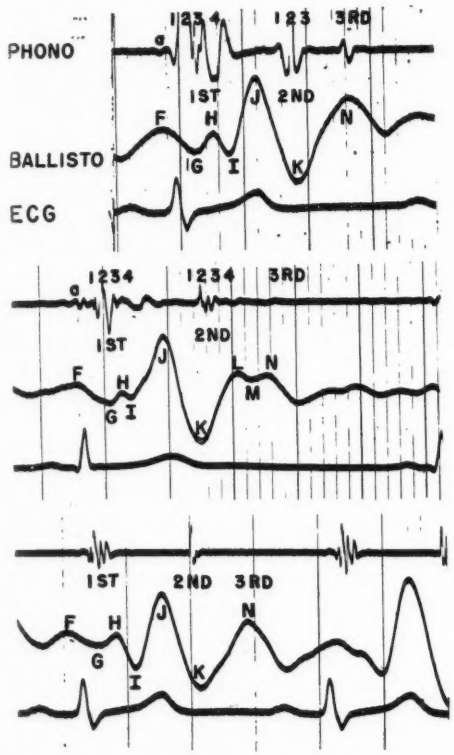

FIG. 2. Simultaneously registered phonocardiograms, ballistocardiograms and electrocardiograms which show: (1) The ballistic F wave is related to the auricular sound of the phonocardiogram. (2) The ballistic G wave occurs with the opening of the semilunar valves. (3) The ballistic H wave is related to the fourth component of the first heart sound. (4) The ballistic I wave occurs with the terminal portion of the fourth component of the first heart sound. (5) The ballistic J wave occurs with the early coarse vibrations in systole. (6) The ballistic K wave is related to the closure of the semilunar valves. (7) The ballistic L wave is related to the opening of the atrioventricular valves. (8) The ballistic N wave corresponds to the rapid inflow phase of the third heart sound. Camera speed, 75 mm. per second.

I Wave. The ballistic I wave seems to register at the end of the fourth component of the first heart sound (fig. 2). The I wave appears to terminate with the coarse vibrations in the apex cardiogram which denote systolic activity, or, in a different apex configuration, it may occur at the end of the maximal ejection phase[8] (fig. 3).

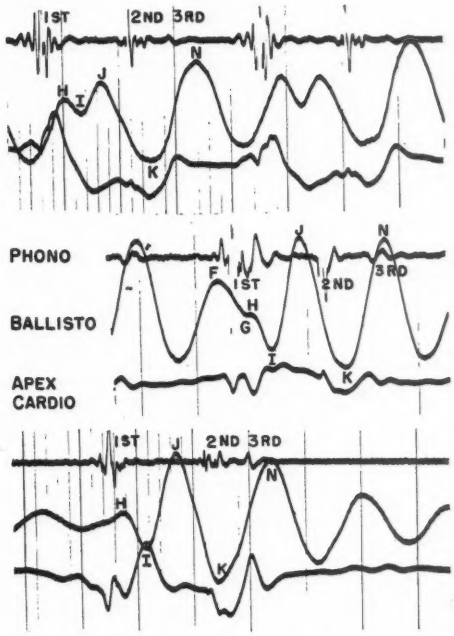

FIG. 3. Simultaneously registered phonocardiograms, ballistocardiograms and apex cardiograms which show their interrelationship. Some inherent phase distortion is evident in the ballistocardiograms. Camera speed, 75 mm. per second.

We have further observed that the ballistic I wave occurs with the anacrotic notch of the surface carotid pulsation and at times slightly delayed, but always occurs prior to the peak of the surface carotid pulse (fig. 4). Similar variation due to respiratory effects or phase displacement was noted in the abdominal aortogram where the ballistic I wave was simultaneous with the beginning of the incisura or occurred within about 0.04 second prior to the incisura (fig. 5). The onset of the femoral surface pulse was roughly simultaneous with

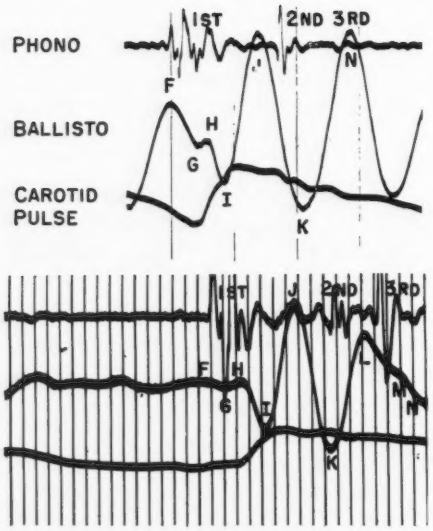

FIG. 4. Simultaneously registered phonocardiograms, ballistocardiograms and carotid pulsations of two subjects with differing heart rates and different degrees of phase distortion. The upper tracing shows more clearly the relationship of the ballistic G wave and the onset of the carotid pulse, the ballistic I wave with the anacrotic notch, and the ballistic K wave with the dicrotic notch of the carotid pulse. Camera speed, 75 mm. per second.

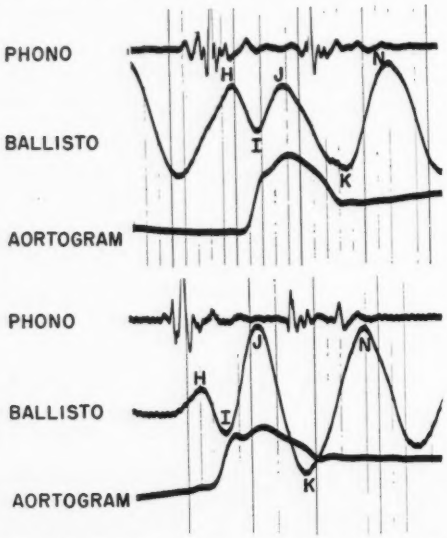

FIG. 5. Simultaneously registered phonocardiograms, ballistocardiograms and abdominal aortic pulsations which show the interrelationships with the ballistic I and J waves. Camera speed, 75 mm. per second.

the ballistic I wave as was observed by Hamilton[16] (fig. 6).

J Wave. The ballistic J wave seems to register with the coarse vibrations in early systole which are generally well registered in the stethoscopic phonocardiogram (fig. 2). In one subject it was found to occur simultaneously with a systolic click in the phonocardiogram. No definite relationship to

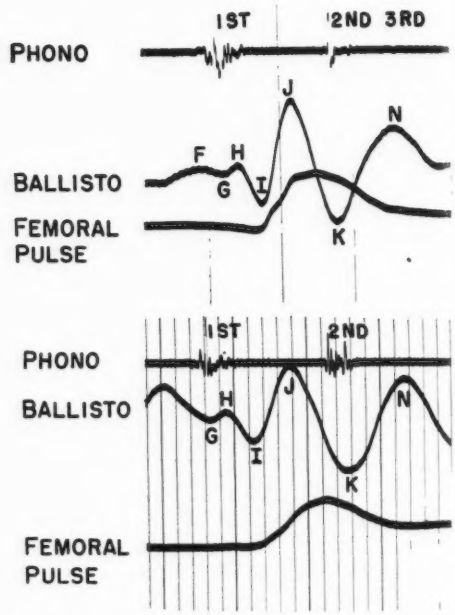

FIG. 6. Simultaneously registered phonocardiograms, ballistocardiograms and femoral pulsations which show the interrelationship of the ballistic I wave and the onset of the femoral pulse, the ballistic M wave and the ascending slope of the femoral pulse, the ballistic K wave and the descending slope of the femoral pulse. Camera speed, 75 mm. per second.

the apex cardiogram has been observed. The ballistic J wave usually is related to the ascending slope of the femoral pulse and roughly with the peak of the carotid and abdominal aortic pulsations (figs. 4, 5, and 6).

K Wave. The ballistic K wave occurs with the second component of the second heart sound[13] which is due to the closure of the semilunar valves (fig. 2). We have not found the ballistic K wave to coincide with the peak

of the femoral pulse as was observed by Hamilton[16] but to coincide with the descending slope of the femoral pulse (fig. 6). The dicrotic notch of the carotid pulse and the peak of the ballistic K wave are usually simultaneous

L Wave. The normal ballistocardiographic patterns were divided into two different groups depending upon the presence or absence of the L and M waves. At times abortive L and M waves could be found, whereas at other times

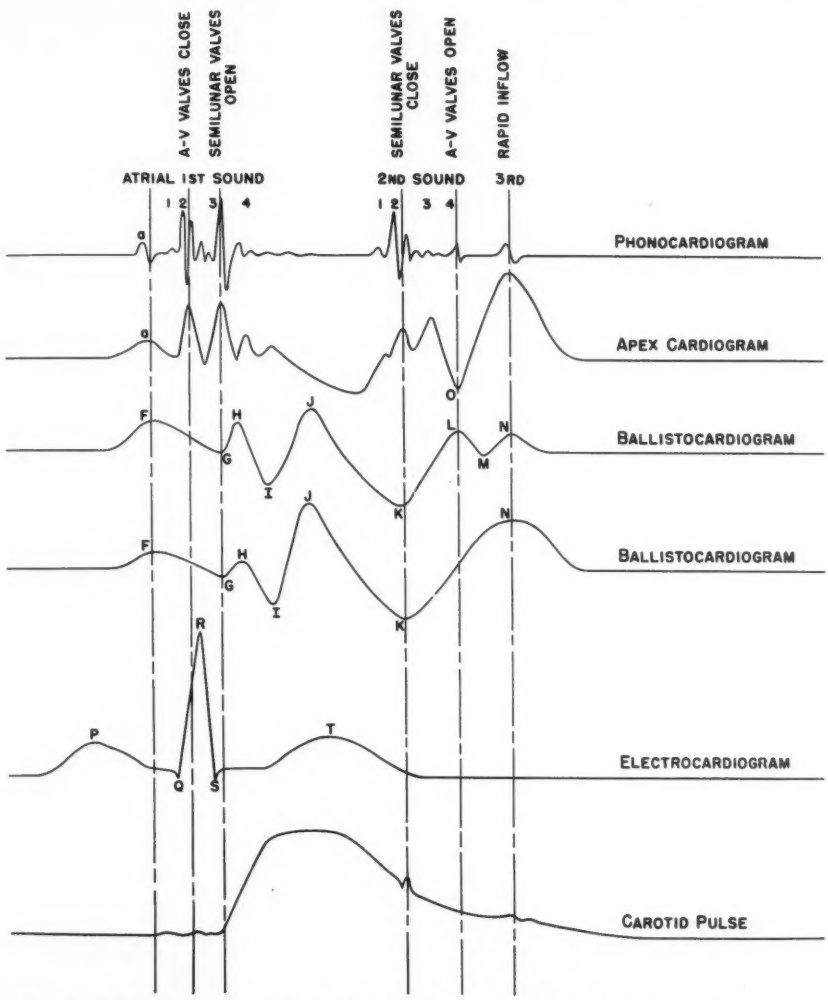

FIG. 7. In view of the fact that no one ballistocardiogram shows all observed interrelationships, a composite pictorial sketch is shown which includes the phonocardiogram, the apex cardiogram, two forms of ballistocardiogram, the electrocardiogram and the carotid pulse.

which is also contrary to Hamilton's[16] observations (fig. 4).

When a split second heart sound was registered, the latter portion of the split sound coincided with the ballistic K wave.

a prolonged K peak was observed. A sharp, "normal" K peak was also observed in the absence of L and M waves.

The ballistic L wave when present coincides in temporal positioning with the fourth com-

ponent of the second heart sound[13] which is the opening of the auriculoventricular valves (fig. 2). This is further confirmed by the fact that the L wave is simultaneous with the negative deflection O present in the apex cardiogram between the peak caused by the closure of the semilunar valves and the peak of the rapid filling wave.[17] The *v* wave of the venous pulse appears to coincide with the ballistic L wave.

M and N Waves. Regardless of the presence or absence of the ballistic L or M waves, the ballistic N wave was found to occur with the third heart sound in the stethoscopic phonocardiogram (fig. 2). Also, the ballistic N wave occurs simultaneously with the peak of the rapid filling wave (fig. 3) or it may be slightly delayed. The slight delay may be explained by the phase shift phenomenon discussed in the first part of this paper.

Discussion

The various peripheral pulsations and the phonocardiograms which were registered on normal subjects in this study indicate that the various component waves of the ballistocardiogram bear a definite relationship to these physiologic events. In some cases, the ballistic waves coincide exactly with the events that are distinctly registered in the sphygmograms and the phonocardiograms. Sphygmographic and phonocardiographic events are reasonably well known and one is definitely tempted to draw conclusions as to the origin of the ballistic waves which tie in so closely. In other cases, the ballistic events do not occur exactly synchronously. In these cases, the natural frequency and degree of damping of the subject were determined. From these values, the approximate degree of phase shift could be estimated. An exact evaluation cannot be obtained as other variables are present which cannot be accounted for. However, when an approximate correction factor is added, the ballistic waves seem to approach a temporal positioning which bears a distinct relationship to the complexes of the sphygmogram and phonocardiogram.

For ballistocardiographic studies it should be possible to devise a table or chart wherein the approximate phase shift that occurs in the subject may be readily determined if the underdamped oscillation is registered by the technic described in part I of this paper. The amount of phase shift that may be present in the instrument may be also compensated for although, as previously discussed, a well designed instrument should introduce minimal distortion of this type.

In view of the fact that no one ballistocardiogram shows all observed relationships discussed in this paper, it was felt that a composite pictorial sketch would be helpful. Two patterns of ballistocardiogram and their relationship to the phonocardiogram, the apex cardiogram and the electrocardiogram are shown in figure 7.

Conclusions

In the ballistocardiograms of normal subjects as registered by the photoelectric displacement type ballistocardiograph, the following observations were made:

1. A positive deflection which precedes the G and H waves was noted which we have arbitrarily named the F wave. It bears a temporal relationship to the auricular sound in the phonocardiogram, to the auricular wave in the apex cardiogram, to the auricular wave in the venous pulse, and to the P and Q waves in the electrocardiogram. These relationships suggest that the ballistic F wave is of auricular origin.

2. The G wave was observed to occur at the time of the third component of the first heart sound on the phonocardiogram, at the time of the second positive deflection in the apex cardiogram, and at the onset of the surface carotid pulse. These physiologic events represent the opening of the semilunar valves.

3. The H wave occurs with the fourth component of the first heart sound. When related to the apex cardiogram, the H wave is temporally related to the various waves denoting systolic activity immediately following the opening of the semilunar valves.

4. The I wave appears to be related to the terminal portion of the fourth component of the first heart sound, and terminates with the

coarse wave components which are related to the first heart sound in the apex cardiogram. The I wave also occurs with the anacrotic notch of the carotid pulse, the beginning of the incisura of the aortogram, and the onset of the femoral pulse.

5. The J wave occurs with the terminal coarse vibrations of systole as indicated by the stethoscopic phonocardiogram and, generally, with the peaks of the carotid pulse and abdominal aortogram.

6. The K wave registers with the second component of the second heart sound and with the vibrations in the apex cardiogram which denote the closure of the semilunar valves. The dicrotic notch of the carotid pulse and the ballistic K wave are also temporally related.

7. The L wave when present occurs at the time of the opening of the auriculoventricular valves as denoted by the fourth component of the second heart sound and by the valley which precedes the rapid inflow phase of blood into the ventricles.

8. The N wave occurs with the third heart sound and with the peak of the rapid filling wave of the apex cardiogram.

9. When displacement type ballistocardiograms are registered simultaneously with other physiologic events on normal subjects, the temporal relationships as discussed may not be exactly simultaneous. The cause is apparently due to phase distortion which occurs in the subject's body and the major corrective factors may be determined by calculation. It is almost impossible with our present knowledge and technics accurately to eliminate all variables as they affect phase displacement in the ballistocardiogram. At best, and until we can completely circumvent all forms of distortion, the timing of the ballistocardiogram with respect to other physiologic events of cardiac origin can only be approximated.

Sumario Español

En este estudio el balistocardiograma normal se interelaciona con varios acontecimientos cardíacos de manera de establecer el oxigen de las ondas componentes. Es aparente que las ondas F, G, H, I, J, K, L, M y N balísticas tienen una relacción definitiva a acontecimientos cardíacos, aunque en algunos casos la posición temporera de los complejos se cambia debido a formas de distorción no controlables. Cuando los factores de corrección se introducen, las ondas balísticas tienden a asumir las relacciones temporeras correctas. Un esbozo gráfico compuesto se presenta que demuestra las relacciones temporeras del fonocardiograma, el cardiograma del ápice, dos formas corrientemente observadas del balistocardiograma normal, el electrocardiograma y el pulso carótido.

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Responses of the Ballistocardiogram in Hypertensive Patients to the Acute Administration of Apresoline, Hexamethonium, Veratrone, Regitine and Sodium Amytal

By DAN C. ROEHM, M.D., ROSS C. KORY, M.D., AND GEORGE R. MENEELY, M.D.

Acute ballistocardiographic responses to five hypotensive drugs have been evaluated in 15 patients with essential hypertension in conjunction with depressor effects. In the majority of experiments qualitative and quantitative ballistocardiographic improvement paralleled the pressure reductions. On occasion the reverse was true. Inferences were drawn from these reactions based on the pharmacodynamics of the drugs. Because of the fundamental nature of the ballistic record, it is concluded that the capacity of the hypertensive heart to respond ballistocardiographically to a depressor agent permits a useful evaluation of its functional reserve and aids in a more physiologic selection of a hypotensive agent.

CLINICAL use of the ballistocardiograph has gained considerable impetus in recent years from the demonstration of a high incidence of abnormal tracings in persons with cardiovascular disease.[1-7] Particularly striking has been the poor prognosis established for persons demonstrating either abnormal contours or amplitudes thought to be associated with low cardiac output.[1] An even higher proportion of persons with heart disease reveal abnormal ballistocardiographic responses when stimuli known to increase cardiac output, such as anoxemia,[8] exercise[9, 10] and eating of meals,[11] are applied.

Nevertheless, the value of the ballistocardiograph is somewhat impaired by the lack of specificity of abnormal records for certain pathologic states. With the possible exception of the pattern associated with coarctation of the aorta,[12-15] no abnormal pattern may be considered to have unique implications. In particular, abnormal ballistocardiographic tracings in hypertensive cardiovascular disease and arteriosclerotic heart disease may be indistinguishable.

Administration of depressor drugs makes it possible to alter the conditions under which the hypertensive heart labors. Ballistocardiographic tracings taken at these times might yield information leading to a better understanding of the etiology of the abnormal record and indicate the efficacy of a given agent in improving the mechanical action of the heart. Although no extended reports of such studies have appeared in the literature, brief mention has been made of ballistocardiographic responses in hypertensive patients who received depressor drugs.[16-18]

METHOD AND MATERIAL

The subjects consisted of 15 male patients all with benign hypertension of several years' known duration and all with initially abnormal ballistocardiograms. The following five drugs were administered parenterally in acute experiments with serial ballistocardiograms and blood pressure determinations: Apresoline, Hexamethonium bromide (C-6), Veratrone, Sodium Amytal, and Regitine.

Apresoline (1-hydrazinophthalazine, C-5968), is a recently introduced hypotensive agent which has been shown to increase renal blood flow, heart rate, and cardiac output while lowering arterial blood pressure.[20, 21] A relatively greater reduction in diastolic pressure has been reported both in dogs[21] and in man.[22] The drug has been found to antagonize certain humoral pressor substances[23-25] and to block vasopressor reflexes from breath holding and immersion of the hand in ice water.[26]

Hexamethonium compounds are anticholinergic

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agents capable of blocking equally sympathetic and parasympathetic ganglia.[27] The sympathetic blockade is manifested by hypotension particularly of the postural variety and relaxation of the peripheral arterioles with increased skin temperature and diminished sweating.[28] Parasympathetic blockade is manifested by decreased salivation and gastric secretion, constipation, and reduced visual accommodation.[29] Cardiac output is either unchanged or slightly decreased following Hexamethonium.[30]

Veratrone, a mixture of alkaloids derived from veratrum viride, is a hypotensive agent whose depressor effect has been ascribed to inhibition of the pressoreceptors of the carotid sinus, of the aortic arch, and of a similar vasodepressor reflex pathway arising in the heart itself.[31, 32] Veratrum in addition produces marked vagal slowing of the heart which can effectively be blocked by atropine without affecting the depressor effect.

Sodium Amytal is known to cause a reduction of blood pressure in some hypertensive patients. This depressor effect has been thought to be of central origin with depression of the vasoconstrictor center and relaxation of peripheral arterioles.[33] On this basis it has been advocated as a testing agent to aid in selection of patients for sympathectomy,[34] but this concept has recently been challenged.[35]

Regitine, 2-[N-p′-tolyl-N-(m′ hydroxy-phenyl)-aminomethyl] imidazoline hydrochloride, C-7337, is a potent adrenergic blocking substance but is less active as a sympatholytic drug.[36, 37] Although some degree of hypotension is obtained in many subjects, this depressor effect is not maintained in most instances.[37] In addition the drug has been shown to decrease coronary flow in the isolated perfused rabbit heart.[36] Regitine at present is used chiefly in the detection and surgical removal of epinephrine-producing tumors.[38]

The ballistocardiograph used in this investigation was of the undamped, high-frequency type with physical properties essentially the same as those of the apparatus originally described by Starr.[39] The patient was permitted to rest 30 minutes on the ballistic table before the control record was taken. All records were made two to four hours after meals. Serial ballistocardiographic tracings were taken and blood pressure variations were recorded at frequent intervals during the course of the experiments. The amount of drug administered and time elapsed were simultaneously noted.

Regitine was administered in a single 5 mg. dose intravenously. The other drugs, diluted in 5 per cent glucose in water, were introduced by slow intravenous drip. The total amount of fluid injected never exceeded 300 ml.; the period of observation ranged from 15 minutes (Regitine) to two hours. No drug was administered within 24 hours of a preceding test. In the case of the four drugs where the dosage was varied (table 1), administration was continued until a significant blood pressure fall, a ballistocardiographic change, or a disagreeable side-reaction was encountered or until the maximum accepted initial dose was reached.

TABLE 1.—*Effects of Acute Intravenous Administration of Each of Five Drugs to 15 Hypertensive Patients. Maximal Blood Pressure Decrease, Increase in Maximum Cardiac Force (Starr), Index of Qualitative Ballistocardiographic Improvement (the Algebraic Sum of Individual Graded Responses) and Dosages of the Drugs Employed*

Drug	Maximum Blood Pressure Fall		Percentage of Change in Maximum Cardiac Force		Index of Qualitative Ballistocardiographic Improvement		Dose of Drug	
	Mean	Range	Mean %	Range %	Mean	Range	Mean	Range
Apresoline	17/18	0/0 to 50/40	+25	0 to +76	+20	0 to ++++	28 mg.	20 to 45 mg.
Hexamethonium	45/20	20/5 to 95/30	+13	−58 to +59	+18	−− to ++++	38 mg.	6 to 65 mg.
Veratrone	41/25	5/5 to 100/40	+15	0 to +58	+20	− to ++++	.11 ml.	.05 to .20 ml.
Na Amytal	51/22	20/5 to 100/20	+16	−41 to +46	+13	−− to +++	700 mg.	300 to 1000 mg.
Regitine	11/12	10/5 to 40/20	+3	−30 to +57	0	−− to +++	5 mg.	5 mg.

The ballistic records were analyzed and classified as to degree of abnormality by the method of Brown and associates[5] and the alterations produced were coded 1 to 4 plus according to the degree of improvement achieved; in instances of worsening a corresponding 1 to 4 minus was recorded. The net results were totaled for each drug to obtain an "index of qualitative ballistocardiographic improvement." Maximum cardiac force per beat[40] was calculated before and after the drug administration. The difference obtained was expressed as percentage of normal based on body surface area. The maximum depressor response occurring at any point during the study was also recorded (table 1).

RESULTS

The mean initial maximum cardiac force per beat for the group was 67 per cent of the predicted. All drugs tested were found capable of improving the ballistic contours in certain patients; none was maximally effective in all. Each patient showed some degree of improve-

ment in the ballistocardiogram with one or more of the drugs. Improvement in the ballistocardiogram occurred in 49 of the 75 experiments or 65 per cent. In only 10 instances did the ballistocardiogram become more abnormal after drug administration, and in an additional 16 the ballistic tracings did not change.

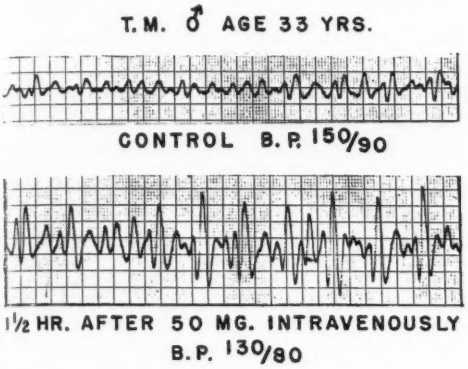

FIG. 1. Ballistocardiographic and blood pressure responses to Apresoline. Note striking increase in amplitude of all waves and more normal contours.

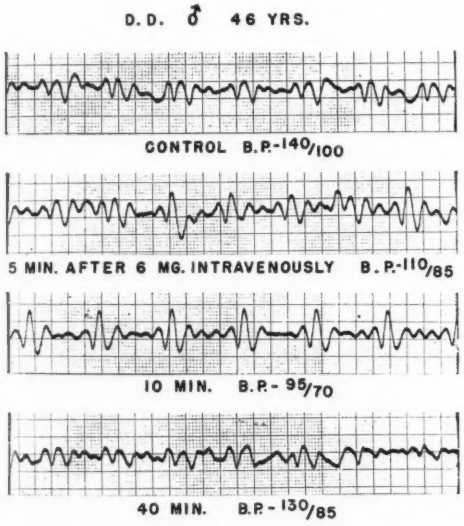

FIG. 2. Ballistocardiographic and blood pressure responses to 6 mg. of Hexamethonium (C6) administered intravenously. The record illustrates improved contours of individual complexes and increased maximum cardiac force. The 40-minute tracing shows regression to a pattern slightly worse than the control, despite some persistent hypotensive effect.

Table 1 summarizes dosage, systolic and diastolic pressure responses, "index of qualitative ballistocardiographic improvement," and percentage of change in maximum cardiac force for each drug. In the dosages employed, the relative ability of these drugs to produce a fall in blood pressure irrespective of the duration of the effect is as follows (listed in decreasing order): Sodium Amytal, Veratrone, Hexametho-

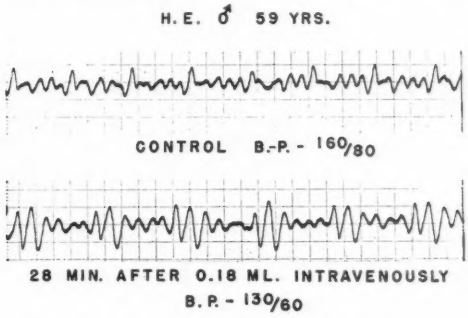

FIG. 3. Ballistocardiographic and blood pressure responses to Veratrone. Note qualitative improvement in ballistic contours.

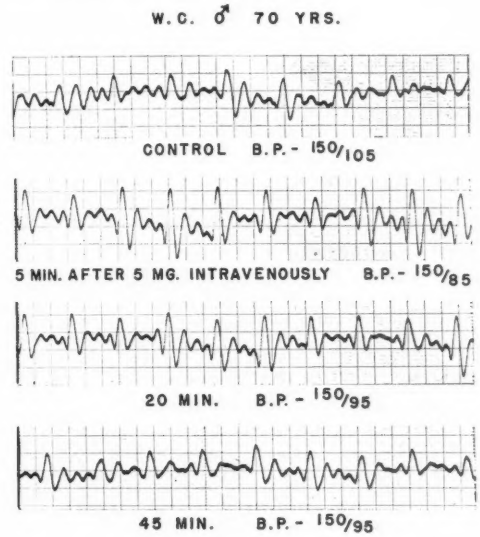

FIG. 4. Ballistocardiographic and blood pressure responses to Regitine. The conspicuous ballistic improvement here is associated with a definite lowering of diastolic pressure, no change in systolic pressure. By 45 minutes the ballistocardiogram has returned to the control pattern.

nium, Apresoline, and Regitine. With respect to qualitative improvement in the ballistocardiogram the order is: Apresoline and Veratrone, Hexamethonium, Sodium Amytal, and Regitine; with regard to improvement of the maximum cardiac force, the following is the order: Apresoline, Sodium Amytal, Veratrone, Hexamethonium, and Regitine. Although ballistocardiographic improvement tended to parellel the hypotensive response, this was not invariable; in certain instances a fall in blood pressure provoked further ballistic abnormality. The diastolic pressure fall was more generally correlated with ballistic improvement, but this was by no means constant. In some instances large falls in diastolic pressure were associated with deterioration of the ballistocardiogram. Conversely striking ballistic improvement sometimes occurred with no change or a slight rise in diastolic pressure.

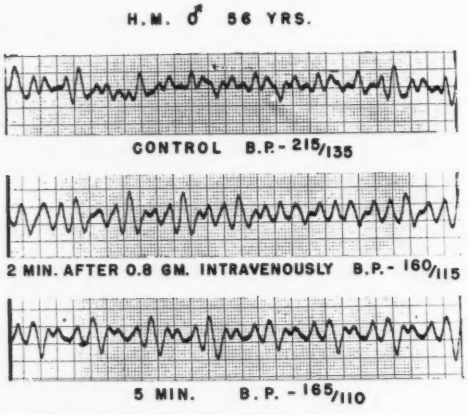

FIG. 5. Ballistocardiographic and blood pressure responses to 0.8 Gm. of Sodium Amytal intravenously. The qualitative form of the tracing is improved sufficiently to be considered relatively normal in the five minute record.

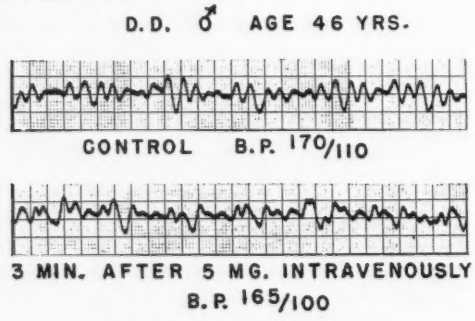

FIG. 6. Ballistocardiographic and blood pressure responses to the standard dose of Regitine. Although depressor response is minimal, the initially abnormal ballistocardiogram shows considerable deterioration particularly in I and J wave amplitude and contours.

Figures 1 to 6 illustrate ballistocardiographic responses to each drug employed.

DISCUSSION

In 1943, Taylor and Page,[41] observed hypertensive patients as a group to have low-output type ballistocardiograms and found that administration of an angiotonin-inhibitor preparation caused a striking improvement in ballistocardiographic contour and output. Conversely, administration of angiotonin in acute experiments to normal subjects produced records similar to those of hypertensive patients. Because tyramine and methyl guanidine, known vasoconstrictors, did not produce ballistocardiograms similar to those of hypertension or those following angiotonin administration, they concluded that these agents were not instrumental in the genesis of renal hypertension. Of the drugs studied in the present series, only Apresoline is known to antagonize angiotonin[42] and this drug although fourth-ranking as a hypotensive agent at the dosages employed, was the most effective in improving the ballistocardiogram. Thus, it appears that Apresoline may exert its beneficial effect partly in ways other than by lowering systemic blood pressure. In no instance did it produce adverse effects on the ballistocardiogram in contrast to all other agents tested. Experience in therapy of several months duration with this drug indicates that this effect is persistent.

Hexamethonium, a potent vasodepressor, although capable, on occasion, of causing remarkable reversions toward normal in the ballistic record (fig. 2), caused increased abnormality in 4 of 15 records. When it is considered that Hexamethonium, through its action of ganglionic blockade,[27] causes peripheral pooling of blood, it is possible that decreased venous return to the heart may have diminished diastolic filling. Such diminished filling as seen in the expiratory phase of respiration has been

considered responsible for complexes of poor amplitude and quality in a heart otherwise capable of producing normal complexes.[43]

With the possible exception of the veratrum alkaloids which have some structural resemblance to digitalis[32] none of the agents used has a direct myocardial action. Sodium Amytal, the most effectively hypotensive drug in the present study, has been considered to produce hypotension as the result of a decrease in peripheral resistance. Winchell and co-workers,[35] however, have recently ascribed this to reduced cardiac output from ballistocardiographic experiments. In patient H. M. (fig. 4), a reduced cardiac output is not suggested ballistocardiographically following administration of Sodium Amytal. Accordingly, administration of the drug was repeated and accompanied by cardiac catheterization. The resting cardiac output was determined by the direct Fick principle to be 6.07 L. per minute initially and 6.02 L. per minute 45 minutes after intravenous administration of the drug, at which time the blood pressure had decreased from 194/120 to 165/100.

Regitine, primarily an antagonist of epinephrine-like compounds,[36, 38] was on occasion quite active ballistically in several patients who had no depressor response suggestive of the presence of an epinephrine secreting tumor (figs. 4 and 6).

The increased maximum cardiac force (IJ amplitude) seen after administration of these drugs stands in contrast to a lack of similar response to exercise in hypertensives as a group.[9] This would seem to indicate that the drugs have enabled the heart to eject blood in a more normal manner rather than imposing an increased demand upon the heart. From the demonstration of Starr[40] the IJK waves of the ballistocardiogram agree in form with the rate of change of acceleration of cardiac ejection, greater amplitudes of IJ, for a given stroke volume, indicate a more nearly normal early acceleration of the blood. In the present study of initially abnormal records where the Starr formula for calculation of stroke volume cannot be applied, no statement can be made with certainty as to cardiac output.

The significance of the achievement of a more normal cardiac ejection form is on a much firmer basis. In those instances in which marked ballistic improvement accompanies a hypotensive response, it is reasonable to ascribe the original abnormality to the handicap arising from the large work requirement.

Failure of the ballistocardiogram to improve despite a hypotensive response is less easily understood. Several possibilities might be considered: (A) Reduced coronary flow secondary to lowered perfusion pressure. In animals, Apresoline, Sodium Amytal, Hexamethonium, and veratrum alkaloids lower blood pressure without decreasing coronary blood flow.[20, 44-46] It is apparent that in abnormal human hearts, factors favoring diminution of coronary flow (notably reduced perfusion pressure) might well outrun other actions of the drugs tending to maintain coronary flow. (B) Pooling of blood and impaired venous return as a result of peripheral vasodilatation. Correlation of the unimproved ballistocardiograms with the rate and magnitude of blood pressure fall indicates that 6 of the 26 unimproved ballistocardiograms could conceivably be explained by peripheral pooling or lowered coronary artery perfusion pressure. Three of these were responses to Hexamethonium, two to Sodium Amytal and one to Veratrone. (C) Direct deleterious effect of the drug upon the myocardium. There is no evidence in the literature of these drugs to support this in the dosages employed. (D) Lack of sufficient cardiac reserve to take immediate advantage of a decrease in work load. The condition of the myocardium in a given patient with hypertension is the resultant of a multiplicity of factors both mechanical and metabolic. This seems to be the most attractive hypothesis: that some hearts do not have sufficient reserve to improve the character of systolic ejection, at least during the period of observation in these acute experiments. If this latter mechanism is operative, the ballistocardiographic responses to depressor drugs should prove of increasing value in assessing myocardial reserve in patients with hypertensive cardiovascular disease.

Summary and Conclusions

1. The ballistocardiographic effects of five hypotensive drugs have been studied in 75

acute experiments in patients with essential hypertension.

2. Initially, as has been found characteristic of hypertensive patients, the records revealed low cardiac output with decreased maximum cardiac force and complexes of abnormal form.

3. Upon administration of depressor drugs, improvement of the ballistic tracings was frequently obtained (65 per cent of experiments) which often, but not invariably, paralleled the hypotensive response. In certain instances, hypotensive responses were associated with increasing abnormality in the tracings for reasons discussed.

4. From the ballistic response of the individual to a given agent and the known pharmacodynamics of the drug administered, insight may be obtained as to how the circulation of the individual hypertensive patient is affected beyond that afforded by blood pressure determinations. As a corollary, the ability of a particular heart to respond to the new milieu created by the various drugs allows further functional evaluation of that heart.

5. In view of the unfavorable prognosis that has been established for patients with abnormal ballistocardiographic patterns, consideration of the ballistocardiographic improvement achieved may rank in importance with the hypotensive response in selection of a hypotensive drug.

Acknowledgment

The authors are indebted to Eva R. Dorris, R.N. for her valuable assistance in this study.

Sumario Español

Cambios agudos balistocardiográficos producidos por cinco drogas hipotensoras han sido evaluados en 15 pacientes con hipertensión esencial en conjunción con los efectos depresores. En la mayoría de los experimentos mejoría balistocardiográfica cualitativa y cuantitativa fué paralela a la reducción en presión. En ocasiones el reverso ocurrió. Inferencias se dedujeron de estas reacciones basadas en la farmacodinámica de las drogas. Por la naturaleza de un record balístico, se concluye que la capacidad del corazón hipertenso a responder balistocardiográficamente a agentes depresores permite la evaluación provechosa de la reserva funcional y ayuda en la selección de un agente hipotensor de un modo más fisiológico.

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Phenolic Compounds in the Treatment of Rheumatic Fever

II. The Metabolism of Gentisic Acid and the Ethanolamide of Gentisic Acid

By NORMAN E. CLARKE, M.D., AND ROBERT E. MOSHER, PH.D.

The absorption and excretion of gentisic acid has been studied to help clarify the confusion that exists in the literature. Data are given that support the retarding action of methyl cellulose and Benemid and also the manner in which these compounds are metabolized in the human body. The first metabolic study of the ethanolamide of gentisic acid in human subjects is described. Evidence is presented that the antirheumatic property of certain phenolic compounds may be explained by the phenomena of chelation and the possible existence of a reversible hydroquinone-quinone system in the blood stream.

THE PUBLISHED REPORTS on the absorption and excretion of the gentisates in man and in animals are conflicting and incomplete and this confusion has been produced in a large part by the methodology employed for the quantitative estimation of this compound.

As early as 1895, Likhatscheff[1] demonstrated that the oral administration to dogs of gentisic acid and ethyl gentisate, produced an elevation of the urinary ethereal sulfates. He estimated that 18 per cent of the ingested gentisic acid and 46 per cent of the ethyl gentisate was excreted in the urine as ethereal sulfates. Later, Neubauer and Falta,[2] working with normal human subjects concluded that 15 per cent of ingested gentisic acid was excreted in the urine as ethereal sulfate while Meyer and Ragan[3] found that 25 per cent of the ingested gentisic acid was excreted unchanged in the urine and that the blood level of gentisic acid was not detectable in people who had ingested as much as 10 Gm. of the drug within 24 hours. In a recent paper, Consden and Stanier[4] claim that 90 per cent of ingested gentisic acid was recovered unchanged from the urine. Paper chromatograms of urines from patients with rheumatic fever and Still's disease, who were treated with gentisates, showed small amounts of conjugates of gentisic acid as well as phenolic conjugates along with free salicylic acid.

Roseman and Dorfman[5] have reported that 61 to 77 per cent of ingested gentisic acid was excreted in the urine within 24 hours and that hydrolysis of the urine by the addition of sulfuric acid and boiling did not increase the free gentisic acid content, so they concluded that no conjugates were present. In rabbits that were fed sodium gentisate, Benati and his coworkers[6] found that sodium gentisate was excreted by the kidneys and without an increase in urinary ethereal sulfates, glucuronic acid or glycine. Meyer and Ragan[3] have reported no increase in urinary glucuronic acid in patients receiving gentisate therapy while Schaefer[7] found a reducing substance in the urine which "at least in part was a glucuronide." These conflicting reports raise doubts as to the validity of the laboratory procedures used in the quantitative estimation of gentisic acid and its derivatives.

We have studied the metabolism of sodium gentisate and gentisic acid in human subjects in an effort to clarify this problem. The acid and the sodium salt behave alike and since the

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The sodium gentisate and methyl cellulose-sodium gentisate tablets used in this study were supplied through the courtesy of Sutliff and Case Co., Inc., Peoria, Ill., the ethanolamide of gentisic acid by the Panray Corp., New York City, and the Benemid by Sharpe & Dohme, Inc., Glenolden, Pa.

sodium salt is more readily available it was used in this study. Our investigation has been extended to consider the metabolism of the ethanolamide of gentisic acid as no report has been published on the fate of this compound in the body.

Methods

The gentisic acid levels were determined quantitatively by the colorimetric procedure of Gerald and Kagan.[8] This method depends upon the blue color formed by the reaction of gentisic acid with an acid solution of ferric and ferrous chlorides. The method is reproducible and reliable. Urine samples were

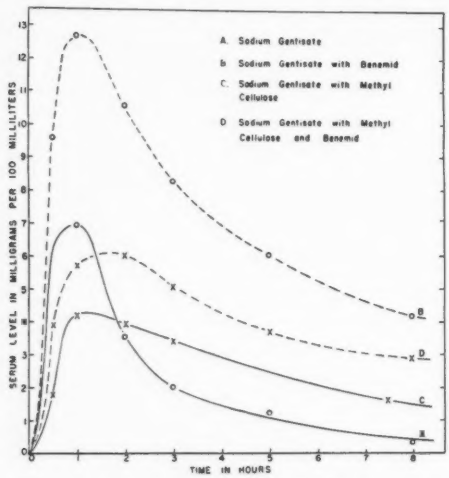
A Sodium Gentisate
b Sodium Gentisate with Benemid
C Sodium Gentisate with Methyl Cellulose
D Sodium Gentisate with Methyl Cellulose and Benemid
SERUM LEVEL IN MILLIGRAMS PER 100 MILLILITERS
TIME IN HOURS

Fig. 1. Blood serum levels of sodium gentisate after the administration of a single dose with and without methyl cellulose and Benemid.

diluted 50 times with distilled water and the blood sera were measured after deproteinization with a tungstic acid solution. All of the density measurements were made at a wave length of 620 millimicrons with an Evelyn photoelectric colorimeter.

Methods that are based upon an ultraviolet absorption at 320 millimicrons or on the reducing power of gentisates (Folin-Ciocalteu reagent, for example) were avoided since we believe they are not sufficiently specific to differentiate between gentisic acid and its possible conjugates. The colorimetric standards for gentisic acid and sodium gentisate in serum and urine were based upon standard solutions of pure gentisic acid. It was found that the same procedure gave accurate results though a less intense color for the levels of the ethanolamide of gentisic acid. The standards for the determination of the ethanolamide were based upon standard solutions of the pure compound.

The urinary glucuronic acid levels were determined by the Tollens' or naphthoresorcinol colorimetric method as modified by Fishman and his co-workers.[9] While it would appear that all of the current methods for the determination of glucuronic acid are in considerable error, we believe this procedure to be the most reliable.

The urinary ethereal sulfate levels were determined by the procedure of Hawk, Oser, and Summerson.[10] The sulfate in 1 aliquot of urine is precipitated by barium chloride and is then filtered, washed, dried and weighed. Another aliquot is then acidified with hydrochloric acid and boiled to hydrolyze sulfate esters. The difference between these two values is then converted to millimoles of sulfate per 24 hours and is termed "ethereal sulfate." All pH determinations were made with a Beckman line-operated pH-meter (Model H-2) using glass and calomel electrodes. The absorption spectra were determined with a Beckman Model DU Quartz Spectrophotometer using 1 cm. fused silica cells. All of the values listed for the concentrations of these components in the urine are given in millimoles which makes it possible to compare directly the drug, glucuronic acid and ethereal sulfate levels. Standard deviations are given rather than average deviations.

Results

The Absorption of Gentisates

The rapidity of absorption of a substance from the gastrointestinal tract may be determined by measuring the time before it appears and also reaches its peak level in the blood stream. We found that a measurable amount of gentisate appears in the blood stream within 15 minutes after its oral administration. This observation is of qualitative value only since the exact magnitude of the level reached in this period will depend, among other things, upon the form in which the compound is administered. Our tests made with gentisic acid ethanolamide and sodium gentisate with and without Benemid, and with tablets compounded of sodium gentisate and methyl cellulose confirm this statement.

In most patients the blood serum level reached its peak within one hour, while a few patients required twice as long. Figure 1 shows the blood serum gentisate levels after the ingestion of 33 mg. of sodium gentisate per kilogram of body weight. All data presented in this figure were obtained on the same individual. Combinations of sodium gentisate with Ben-

mid and with methyl cellulose were tested to note any retarding influence on the blood levels. The methyl cellulose was incorporated directly with sodium gentisate in compressed tablets for the purpose of delaying its absorption and thereby obtaining a more constant blood level. The patient was "conditioned" with 2 Gm. of Benemid every 24 hour period for several days before the tests were performed. The maximum blood concentration occurred one hour after ingestion of the drug and then dropped off rapidly. The lower blood serum levels obtained with the tablets containing methyl cellulose indicate a retarded absorption from the gastrointestinal tract. It appears evident that Benemid helps to maintain a higher blood level and for a longer time. Although the blood serum levels are higher after any given interval of elapsed time when Benemid is used, a more constant level is maintained by the combination with methyl cellulose. There is a linear relationship between the dose of gentisate administered and the blood serum level attained under any given set of circumstances.

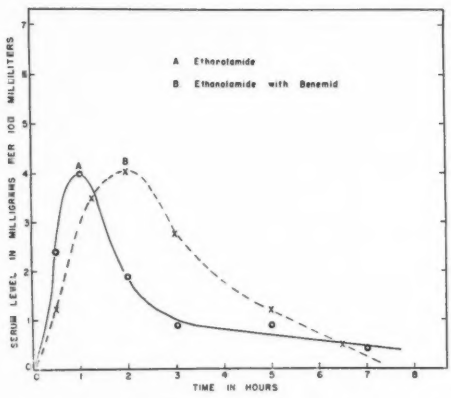

FIG. 2. Blood serum levels of the ethanolamide of gentisic acid after the administration of a single dose with and without Benemid.

In figure 2 is presented data from a similar study in which the ethanolamide of gentisic acid was administered alone and in combination with Benemid. It is significant that Benemid causes a displacement but no elevation of the gentisate blood level curve. Presumably the action of Benemid may be associated with the presence of a free carboxy group in the drug.

The Excretion of Gentisates

The gentisates are eliminated rapidly from the body. A measurable amount of gentisate can be detected in the urine within 30 minutes after its oral administration. Table 1 presents the 24 hour excretion data from a number of rheumatic fever patients who were treated with various gentisates alone and also in combination with Benemid or methyl cellulose.

TABLE 1.—*Twenty-four Hour Excretion of Gentisates*

Drug	No. of Patients	No. of Samples	Ave. % Excreted*	Std. Dev.
Sodium gentisate	8	28	58.3	±14.8
Gentisic acid	4	16	60.9	±18.1
Ethanolamide (adults)	3	19	25.8	± 6.3
Ethanolamide (children)	3	29	44.1	±11.1
Ethanolamide and Benemid (adults)	2	12	35.5	± 5.9
Ethanolamide and Benemid (children)	5	37	23.5	± 9.5
Sodium gentisate and methyl cellulose	4	30	61.7	±13.9

* Free Drug.

TABLE 2.—*The Excretion of Total and Free Gentisate*

Patient	Drug	No. of Samples	Ave. $\left(\frac{\text{Total Drug}}{\text{Free Drug}}\right)$
M. L.	Sodium gentisate	10	1.11 ± 0.03
R. S.	Ethanolamide of gentisic acid	7	2.09 ± 0.24

The excretion, although high, is never entirely complete for reasons as yet unexplainable. Less than 1 per cent of the drug is excreted through the bowel. The authors believe that occasionally this missing fraction has resulted from drug buildup in body fluids or tissues since in some patients with pleural effusion, the pleural fluid contained from 5 to 6 mg. of drug per 100 ml. The excretion of the ethanolamide of gentisic acid is much lower than that of sodium gentisate. There is no correlation between the urine volume and pH, and the drug output for a 24-hour period.

Evidence that conjugates of gentisic acid occur as metabolic end-products is presented in table 2 which lists the ratios of total to free gentisate found in the 24-hour urines of rheumatic fever patients who were treated with sodium gentisate and with the ethanolamide of gentisic acid. The total drug levels were determined by applying the colorimetric method for gentisates to aliquots of urine which had been hydrolyzed by boiling with dilute hydrochloric acid.

It appears from these data that a certain amount of both drugs is "bound" in the urine and can be liberated only by an acid hydrolysis. Although the bound portion is low with sodium gentisate, it appears in significant amounts with the ethanolamide. The nature of this conjugate fraction has not been established with certainty but it may conceivably exist in one or all of three different forms; namely, as ethereal sulfates, glucuronides or as the glycine derivative.

Table 3 presents data on the daily excretion of glucuronic acid and ethereal sulfate by rheumatic fever patients who were treated with the ethanolamide of gentisic acid, sodium gentisate and of both compounds in combination with Benemid. The Benemid was given for a few days before the gentisate compound was administered.

There is a distinct increase in the urinary excretion of ethereal sulfate and glucuronic acid after the ingestion of the ethanolamide of gentisic acid but these urinary metabolic products are not increased by the ingestion of Benemid alone. In the rheumatic fever patient treated with sodium gentisate there is a correlation between the millimoles of total drug, ethereal sulfate and glucuronic acid excreted in the urine. However, there is no direct relationship between the total drug and the conjugates excreted in the urine when the patient received both sodium gentisate and Benemid although the levels of the conjugates are higher but without a definite ratio pattern.

Table 4 presents data from a patient with rheumatic fever who was treated with the ethanolamide of gentisic acid and whose urine showed an elevated excretion of glucuronic acid and ethereal sulfate. The total excretion of these two components is approximately equal to that of the combined drug, which implies the existence of only two major conjugates. It is significant that the ethereal sulfate output is considerably higher for the ethanolamide of gentisic acid than for sodium gentisate.

A number of eight-hour excretion tests were run after the administration of a single dose of gentisate and representative data are given in figures 3 and 4. If sulfates and glucuronides of gentisates are formed in the body, the rise and fall in excretion of these constituents in an eight-hour period should parallel the rise and

TABLE 3.—*The 24-Hour Urinary Excretion of Ethereal Sulfate and Glucuronic Acid Following the Ingestion of the Ethanolamide of Gentisic Acid, Sodium Gentisate and in Combination with Benemid*

Drug	Daily Intake (millimoles)	No. of Days	Ave. 24 Hour Excretion (Millimoles)		
			Total Drug	Ethereal Sulfate	Glucuronic Acid
None	0	6	—	0.89 ± 0.31	1.31 ± 0.64
Ethanolamide	40.6	10	—	10.7 ± 1.3	9.7 ± 2.3
Ethanolamide and Benemid	40.6	6	—	9.0 ± 1.7	14.1 ± 3.6
None	0	4	—	0.95 ± 0.25	0.50 ± 0.20
Ethanolamide	30.4	9	—	5.4 ± 1.0	9.0 ± 1.2
None	0	4	—	1.5 ± 0.13	0.45 ± 0.38
Benemid alone	2 Gm.	4	—	1.0 ± 0.16	0.76 ± 0.27
None	0	4	0	0.38 ± 0.11	0.91 ± 0.23
Sodium gentisate	11.4	2	5.4	1.41	1.90
Sodium gentisate	17.0	1	5.8	1.56	1.05
Sodium gentisate	34.1	9	13.7 ± 2.8	2.42 ± 0.91	2.11 ± 0.97
Sodium gentisate and Benemid	34.1	3	16.7 ± 1.8	4.09 ± 0.60	2.71 ± 1.29
Sodium gentisate and Benemid	45.4	10	16.4 ± 5.0	4.78 ± 1.14	2.11 ± 0.97
Sodium gentisate and Benemid	39.8	13	10.2 ± 5.0	4.60 ± 0.96	4.54 ± 1.42

fall of the total drug excreted during this same period. This is suggested by the curves for the urinary excretion of the ethereal sulfate, glucuronic acid and for the total drug, which is additional evidence that conjugates of gentisates are formed.

A further phenomenon, worthy of mention, is the frequent occurrence of dark urines from patients being treated with the gentisates. Usually, this color formed in the urine after it had been exposed to the air for some time, but occasionally the urine was dark when voided. Similar results have been reported in human subjects and animals following the ingestion of salicylates or gentisates.[1, 11, 12] In many respects these urines resemble alkaptonuric urines in that they darken from the top down, and only in the presence of atmospheric oxygen. The darkening process may be inhibited by the addition of ascorbic acid. As pointed out by Abbott and Salmon[11] and by Blum,[13] the distinctive color cannot be due to homogentisic acid. The most reasonable explanation is that this color change is due to the presence of the quinone of gentisic acid. The light absorption curve of the dark gentisate urines is essentially the same as that of the air-oxidized gentisic acid solution as is demonstrated in figure 5. It was found that the gentisate-treated patients' urines darkened more rapidly upon exposure to air than did the solutions of gentisic acid. The gentisic acid solutions at a pH of 6.6 could be exposed to air for as long as six weeks without appreciable darkening, but many urines from patients on gentisate therapy started to oxidize or darken within two to three days. It seems probable that the urine contains a catalyst for this oxidation process and that it must also contain an antioxidant since not all urines of patients on gentisate therapy darkened immediately. Figure 6 demonstrates the change in density of various dilutions of urine from an untreated normal male adult to which had been added the same amounts of gentisic acid. All solutions were adjusted to definite pH values. At pH values of 5 and 7, the gentisates alone did not air-oxidize appreciably. However, when urine was added at dilutions as low as 1 part of urine to 100 parts of the final solution, accelerated darkening was apparent. These results suggest that the ascorbic acid normally present in urine protects the gentisate from oxidation for a short period, but that when the ascorbic acid has been oxidized, a catalyst or enzyme in the urine produces the rapid oxidation of the gentisate to the quinone form. At a pH of 10, rapid oxidation occurs from the start of the experiment. At

TABLE 4.—*Twenty-four Hour Excretion Study of the Ethanolamide of Gentisic Acid*

M. moles Ingested Drug	24 Hour Urinary Excretion in Millimoles					
	Total Drug	Free Drug	Comb. Drug	Gluc. Acid & Ether. Sul.	Ethereal Sulfate	Glucuronic Acid
54.1	33.9	16.7	17.2	18.6	7.43	11.1
54.1	37.0	20.2	16.8	21.4	9.06	12.3
54.1	24.8	11.7	13.1	13.8	5.74	8.1
54.1	51.5	22.8	28.7	24.7	10.59	14.1
54.1	50.6	31.8	18.8	23.6	9.86	13.7
54.1	35.5	13.4	22.1	14.0	6.75	7.2
54.1	37.9	15.8	22.1	21.5	8.55	12.9
54.1	32.4	11.2	21.2	—	—	12.8
54.1	37.7	15.3	22.4	25.7	10.85	14.8
54.1	20.8	9.3	11.5	10.5	2.73	7.8
54.1	12.6	5.7	6.9	6.8	3.93	2.9

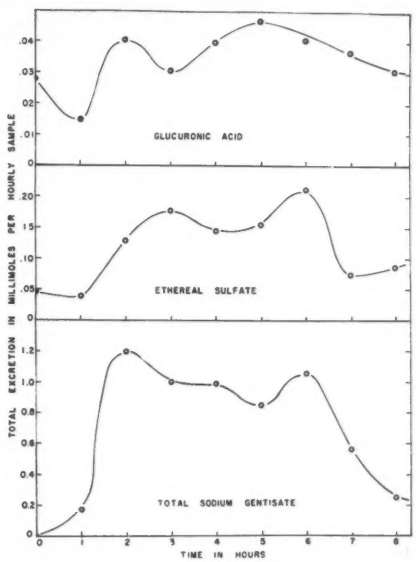

FIG. 3. The eight-hour excretion of sodium gentisate, glucuronic acid and ethereal sulfate.

this alkalinity the oxidation-reduction potentials of gentisic acid or the natural anti-oxidants of urine or of both are so modified that they fail to protect gentisic acid from assuming the

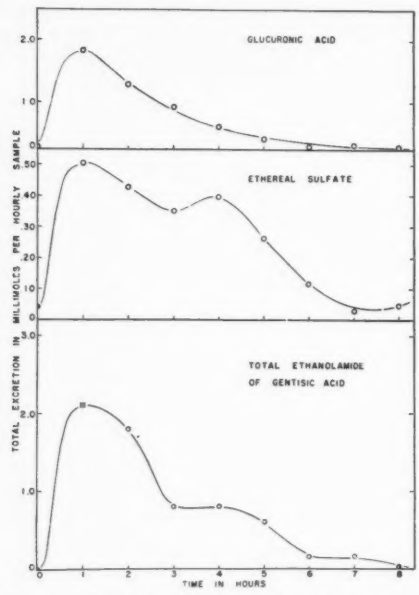

FIG. 4. The eight-hour excretion of the ethanolamide of gentisic acid, glucuronic acid and ethereal sulfate.

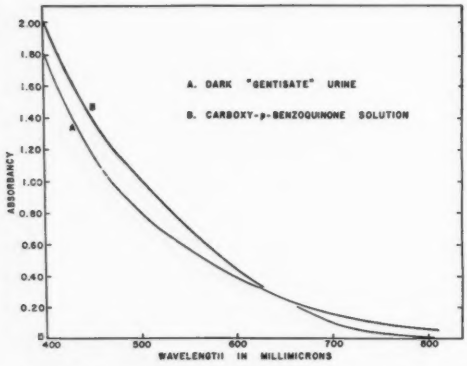

FIG. 5. Absorption spectra of carboxy-p-benzoquinone and of a dark "gentisate" Urine.

quinone form. All urines containing gentisates will darken on exposure to the air, but the length of time required before the darkening becomes perceptible will depend upon the amount of antioxidant (ascorbic acid) present in the urine. Those urines that are deficient in this agent will be dark when excreted or will start to darken shortly after they are excreted.

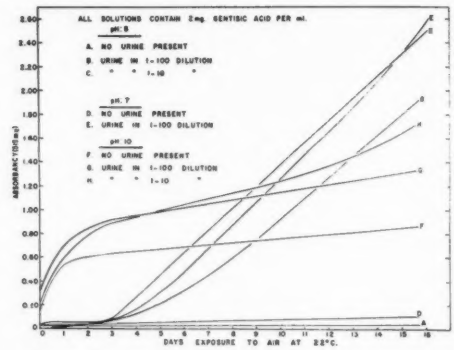
ALL SOLUTIONS CONTAIN 2mg. GENTISIC ACID PER ml.
pH: 8
A. NO URINE PRESENT
B. URINE IN 1-100 DILUTION
C. " " 1-10 "
pH: 7
D. NO URINE PRESENT
E. URINE IN 1-100 DILUTION
pH: 10
F. NO URINE PRESENT
G. URINE IN 1-100 DILUTION
H. " " 1-10 "
ABSORBANCY (700 mμ)
DAYS EXPOSURE TO AIR AT 22°C.

FIG. 6. The darkening of urine containing gentisic acid under various conditions.

DISCUSSION AND CONCLUSIONS

Since gentisic acid or carboxy-p-benzoquinone is structurally related to phenol, hydroquinone, salicylic acid and benzoic acid, it is reasonable to expect that the mechanisms utilized by the body in detoxifying these latter compounds may be involved in the elimination of gentisic acid and the conjugates should be similar, at least qualitatively. Benzoic acid, when administered in small doses, is excreted entirely as hippuric acid, but when given in larger amounts there is some benzoylglucuronic acid as well as a small amount of free acid excreted in the urine.[14] There is evidence that hydroquinone is excreted both as the ethereal sulfate and as a glucuronide,[15] while phenol is excreted as the free compound, the ethereal sulfate, the glucuronide or other conjugates.

According to Kapp and Coburn,[12] 80 per cent of ingested sodium salicylate is excreted in forms containing intact salicylic acid, the most important being glucuronic acid derivatives, free salicylic acid, the glycine derivative and gentisates. Apparently ethereal sulfates are not formed in appreciable quantities.

By comparing these compounds we find that salicylic acid does not form ethereal sulfates as do other phenols and that the amount converted to the glycine derivative is lower than for benzoic acid. This action is apparently due to the chelation or hydrogen-bonding which oc-

urs between the two groups situated in adacent positions on the aromatic ring. It is nown that the increased acid strength of salilylic acid over benzoic acid is due to this chelaion. Since the glucuronide of salicylic acid loes occur it is possible that this means of letoxication may occur despite the chelation. With gentisic acid the ortho placement of groups occurs also and the conjugation prodicts should be similar with respect to this grouping, although some modification may be expected since there is a free hydroxy group in the 5- position which should confer further phenolic properties to gentisic acid. The anticipated metabolic products of gentisic acid are free gentisic acid or gentisates, conjugated gentisic acid or ethereal sulfate, glucuronides, glycine derivatives, and possible oxidation products and their conjugates. The gentisates are among the main oxidation products of salicylic acid in the human body. Schayer[16] working with salicylic acid which was labeled with carbon-14 has shown that salicylic acid and its metabolic products are completely eliminated from the body with no tissue retention. With only an insignificant amount released as carbon dioxide it would appear likely that the above tabulation covers the major possible metabolic by-products of gentisic acid and the conjugated and free form co-exist in the urine. The presence of glycine derivatives is doubtful. Since an occasional patient will void a dark urine, it is reasonable to include carboxy-p-benzoquinone, in the list of metabolites. This last component does not occur ordinarily in the urine although the work of Heubner[17] on the reversible oxidation and reduction of hydroquinones in blood strongly suggests that the quinone of gentisic acid does exist in the body. Whether this has any bearing on the antirheumatic action of the gentisates is at present a moot question.

There may be a correlation between the chemical structure of these compounds and their excretion as ethereal sulfates. Salicylic acid, gentisic acid or sodium gentisate and the ethanolamide of gentisic acid differ a great deal in the extent to which they are excreted as sulfates and in the following order: salicylates < sodium gentisate < ethanolamide of gentisic acid. This may be due to the number and the placement of the hydroxy groups. Salicylic acid is reported as not forming ethereal sulfates in human subjects. In this compound the carboxy and hydroxy groups exist in adjacent or ortho positions on the ring, and the hydroxy group is bound so tightly by chelation that it is not available for reaction or coupling with sulfate. With gentisic acid, however, we have an additional hydroxy group in the 5- position which is available and as we have shown this compound does produce an elevation of the urinary ethereal sulfate excretion. With gentisic acid ethanolamide the carboxy group is tied up by a nonionic linkage and although some chelation could occur it is relatively weak when compared with that in the free acid. The net result is that a statistically larger number of hydroxy groups is available for conjugation and the amount of conjugates excreted is increased. As reported by Williams[14] this is true of other amides of phenolic aromatic acids. Von Oettingen[15] explains this phenomenon by saying that the "basic" $—CONH_2$ grouping attracts the "highly acid" $—OSO_3H$ group thus favoring an increase of ethereal sulfates. If this were true, one would expect the $—OSO_3H$ to attach itself to the amide group rather than to a nearby hydroxy group. Furthermore, the $—OSO_3H$ group can hardly be expected to exist as such in the body while sulfate ion itself must be considered to be a base rather than an acid since it is an electron donor rather than an acceptor. It was found by Likhatscheff that ethyl gentisate caused a greater excretion of ethereal sulfates than did gentisic acid. This is in accord with the above explanation since esters of gentisic acid would exhibit weaker chelate bonds than the acid.

Although our evidence for the existence of conjugates of gentisic acid is suggestive rather than conclusive, we know that the actual isolation and positive identification of each conjugate will be a difficult task. Their labile nature poses great difficulties and a definite answer is not expected in the near future.

Summary

The absorption and excretion of gentisates in the human body has been discussed, with

demonstration of the influence of Benemid and methyl cellulose on the gentisate blood serum levels.

Gentisic acid and its ionizable salts are to a small extent excreted as ethereal sulfates and glucuronides as well as the free drug. In some patients the oxidized or quinone form has been present.

A larger portion of the ethanolamide of gentisic acid is excreted as ethereal sulfates and glucuronide conjugates than with gentisic acid itself. This behavior is explained on the basis of differences in molecular structure or hydrogen bonding.

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Sumario Español

La absorción y la excreción del ácido gentísico ha sido estudiada para ayudar a aclarar la confusión que existe en la literatura. Datos se presentan para sostener la acción retardante de la metilcelulosa y Benemid y también la manera en que estos compuestos son metabolizados por el organismo humano. El primer estudio metabólico de la etanolamida de ácido gentísico en sujetos humanos se describe. Evidencia se presenta en favor de que las propiedades antireumáticas de ciertos compuestos fenólicos se puede explicar por el fenómeno de chelación y la posible existencia de un sistema reversible de hidroquinona - quinona en la sangre.

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Cardiovascular Collagenosis with Parietal Endocardial Thrombosis

A Clinicopathologic Study of Forty Cases

By B. J. P. Becker, M.D., B.Ch., C. B. Chatgidakis, M.B., B.Ch., and B. van Lingen, M.D.

Forty cases of endocardial thrombosis of the heart were selected for pathologic study from a total of 9,500 autopsies performed during 1936 to 1951. Widespread focal involvement of the connective tissue throughout the body and particularly in the heart was demonstrated. Although the histopathologic features were similar to those found in the "diffuse collagen diseases" they did not show the characteristic lesions of rheumatic fever, periarteritis nodosa, lupus erythematosus or diffuse scleroderma. The clinical presentation of a rapidly progressive heart failure, together with the pathologic findings, were sufficiently distinctive to consider this condition as a cardiovascular collagenosis with parietal thrombosis. A similar condition has been described under a variety of names and would appear to constitute a large proportion of cases of so-called "idiopathic hypertrophy" or "myocarditis" of the heart.

THE OCCURRENCE of necrosis or fibrosis of the endocardium with overlying mural thrombosis in the absence of gross vascular disease appears to have been first adequately described by Löffler[1] who termed the condition "endocarditis parietalis fibroblastica" and associated it clinically with a syndrome of progressive cardiac failure and eosinophilia. Subsequently, a similar clinicopathological picture was reported under a variety of terms, namely, fibrosis of the endocardium and myocardium with mural thrombosis[2]; endocardial fibrosis[3, 4]; endomyocardial necrosis[5]; primary subacute myocarditis[6]; myocarditis perniciosa[7]; and chronic fibroblastic myocarditis.[8]

In these, eosinophilia was not constant and, if this phenomenon can be regarded as variable, many of the cases of idiopathic heart disease, including Fiedler's myocarditis, reported in the literature may belong in this category.[9–30]

In this paper we report on 40 cases of this clinicopathologic entity and produce evidence which suggests that the condition is due to disturbances of the connective tissues of the heart. It should accordingly be classified as a diffuse collagen disease along with other well recognized types, such as periarteritis nodosa, lupus erythematosus, diffuse scleroderma, and rheumatic heart disease.

From the Department of Pathology, University of the Witwatersrand, Johannesburg, South Africa.

Pathology

The morbid anatomic features in all cases were: (1) Evidence of congestive cardiac failure. (2) Visceral infarction. (3) A characteristic cardiac lesion.

Congestive cardiac failure was the cause of death in all cases and was manifested by edema, ascites, pleural effusions and chronic venous congestion of the viscera.

Solitary or multiple infarction of one or more viscera was found in 78 per cent of patients. In half of these more than one organ was affected. The sites of infarction were as follows: Lungs (25 cases), spleen (6 cases), kidney (18 cases) and brain (3 cases). Infarcts were always bland and were both recent and old. In the majority of cases the cause was clearly embolic.

The cardiac lesion was characterized by: (1) An enlarged, dilated heart, usually without hypertrophy. (2) Mural thrombosis, especially in the left ventricle. (3) Subendocardial necrosis or fibrosis. (4) Fibrosis or necrosis of papillary muscles. (5) Focal or diffuse thickening of the endocardium. (6) Absence of significant lesions in pericardium, cardiac valves, coronary vessels or aorta.

The pathologic features of the heart in 40 cases are summarized in table 1.

Incidence

The incidence of the condition in autopsy subjects is 0.42 per cent (40 cases in 9,500 consecutive autopsies). It occurred at all ages and with equal incidence in both sexes, but was somewhat commoner before the age of 40. Thirty-two cases were Bantu subjects (0.71 per cent) and eight were European (0.18 per cent). This difference is significant statistically.

Table 1.—*Characteristic Features of the Cardiac Lesions*

Site	Morbid Anatomy	Remarks
Pericardium	Moderate excess clear fluid	62% Fibrinous exudate unusual
Heart size	Dilatation of all cavities	93%
Heart weight	340–795 Gm.	Average 504 Gm.
Left ventricle hypertrophy	Absent in 73% When present, history of antecedent hypertension	Measurements within normal limits as a rule, according to criteria of Coggen, Griggs & Stilsen[31]
Right ventricle hypertrophy	Present in 8%	
Mural thrombosis	Left ventricle —100% Left auricle — 75% Right auricle — 59% Right ventricle— 5%	Characteristic finding. Commonest site between papillary muscles of left ventricular apex. Varied in degree
Parietal endocardium	Endocardial necrosis or endocardial sclerosis	Subjacent to thrombus Diffuse or focal
Valvular endocardium	Normal	100%
Myocardium	Subendocardial necrosis or fibrosis	Chiefly subjacent to thrombus
Coronary vessels	Healthy and patent. Occasionally slight atheromatosis	Not significant as a cause of the myocardial lesions
Aorta	Normal Fine intimal wrinkling	92% 8%

In a description of a similar condition Davies[3] found an incidence of 0.95 per cent in 3,759 autopsies on African subjects in Uganda, and the condition accounted for nearly 10 per cent of patients dying of congestive cardiac failure.

Classification

The cases have been arbitrarily divided into acute, subacute and chronic depending upon the histologic features in the heart. The acute cases were characterized by acute mucinous edema, fibrinoid necrosis, increased capillary permeability and "serous" myocarditis, parenchymatous degeneration, polypoid verrucous lesions, and thrombosis. In the subacute phase cellular infiltration and organization of the above-mentioned lesions was the predominant finding to the extent of granuloma formation. Endocardial sclerosis and hyperplasia of the elastic tissue were the outstanding features of the cases classified as chronic.

Histopathology

Methods

The tissues were formol-fixed, dehydrated in alcohol and embedded in paraffin wax. Sections were cut at 4 μ, deparaffinized and stained by the following methods. Metachromasia was demonstrated by either toluidine blue 0.5 per cent in distilled water plus 0.25 per cent borax, or aqueous 0.05 per cent solution of toluidine blue at pH 4.5 as recommended by Bunting[32]; alcohol resistance was tested by the method advocated by Bunting.[32] The reaction of the chromatotropic substance to testis hyaluronidase was tested by the method advocated by Pearse[33]; the reaction to streptococcal hyaluronidase was tested by the application of undiluted filtrate of a 24-hour culture of a Richards-strain hemolytic streptococcus to the sections for three hours, using cartilage meta-

hromasia as a sensitive control. In addition, ections were stained with the periodic acid Schiff reagent of McManus[34] and Hotchkiss[35],

FIG. 1. Section of mural endocardium near the apex of the left ventricle showing polypoid foci of "mucinous edema." Hematoxylin and eosin × 96.

before and after extraction with hot chloroform-methanol for 24 hours, and before and after salivary digestion, and for basophilia the methylene blue extinction test, as recommended by Pearse[36] was used.

Histopathologic Changes

The earliest reaction which has been observed was swelling of the mural endocardium. For reasons which will be elaborated, we have termed this a mucinous edema. With ordinary (hematoxylin and eosin) stains the subendothelial tissues are swollen and occasionally scantily infiltrated with mononuclear cells. This lesion is usually focal so that normal endocardium passes abruptly into edematous, somewhat myxomatous polyps.

In such edematous foci the surface endothelial cells enlarge, their nuclei become darkly staining and their cytoplasm basophilic, and either desquamation or proliferation occurs. These foci of mucinous edema were found especially in the depths of the crypts between the columnae carneae, over the papillary muscles and in the thebesian sinuses. Similar lesions occurred as eccentric foci in the subintimal tissues of the smaller blood vessels of the myocardium but epicardial involvement was rare.

When stained with toluidine blue a marked metachromatic reaction was obtained. Histo-

TABLE 2.—*Results and Significance of Histochemical Tests*

Method	Result	Significance
Toluidine Blue	Red-violet metachromasia	Acid mucopolysaccharides, acid colloidal substances, nucleic acids, polymer formation.[33]
Alcohol resistance	Positive	Most likely acid mucopolysaccharide.[33]
Methylene blue extinction test	Basophilia positive at pH 2.6	Mucopolysaccharides.[38]
Toluidine blue after treatment with testicular hyaluronidase	Metachromasia persists	Suggests chondroitin sulphate A or B.[36]
Toluidine blue after treatment with streptococcal hyaluronidase	Metachromasia persists	Suggests chondroitin sulphate B.[37]
Periodic-acid Schiff reagent (PAS)	Magenta	Polysaccharides (glycogen), mucopolysaccharides, mucoproteins, glycoproteins, glycolipids, phospholipids.[33]
PAS after chloroform-methanol extraction	Positive	Excludes lipids.[33]
PAS after digestion with saliva	Positive	Excludes glycogen.[33]

chemical investigation of this chromotropic material showed that it can be attributed to the presence of an acid-mucopolysaccharide—probably chondroitin sulphate B. (See table 2.)

We can therefore regard this lesion as a true mucinous edema (after Talalajew).[39]

We were unable to obtain this reaction in the normal endocardium or vessels of 12 control hearts and Bunting[32] has also shown that chromotropic material in this situation or in the stroma accompanying the small blood vessels of the heart is slight or absent.

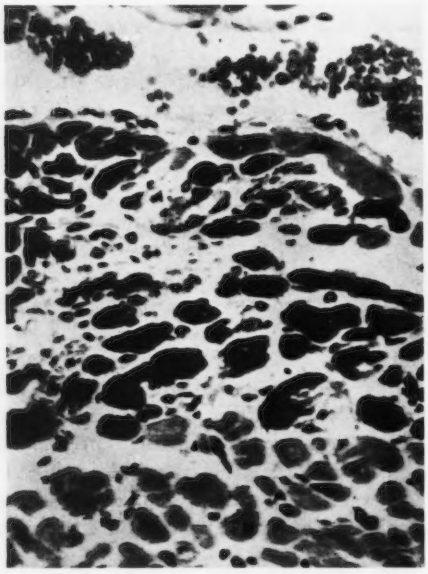

FIG. 2. Section of myocardium of the posterior wall of left ventricle demonstrating basophilic degeneration. Hematoxylin and eosin × 264.

In addition, there was capillary dilatation and stasis, and lesions which we have interpreted as the result of increased permeability of vessels, namely, interstitial myocardial edema, inflammatory cell infiltration and fibrinous exudation.

Interstitial myocardial edema caused wide separation of the muscle bundles and the overall picture resembled the "serous myocarditis" of Eppinger, Kaunitz and Popper.[40] Fibrinous exudation was most marked on the surface of the parietal endocardium, but also occurred in a lesser degree in the endocardial tissues and in the subintimal zones of arterioles and veins, but always in relation to areas of mucinous edema. It was the forerunner of the mural thrombosis and the thrombi which occurred in the thebesian sinuses and luminal vessels.

Focal parenchymatous degenerations, possibly anoxic, occurred chiefly in the inner third of the myocardium, and were both perivascular and paravascular. They consisted of hydropic degeneration, necrobiosis with loss of staining and granular disintegration of fibers, and foc

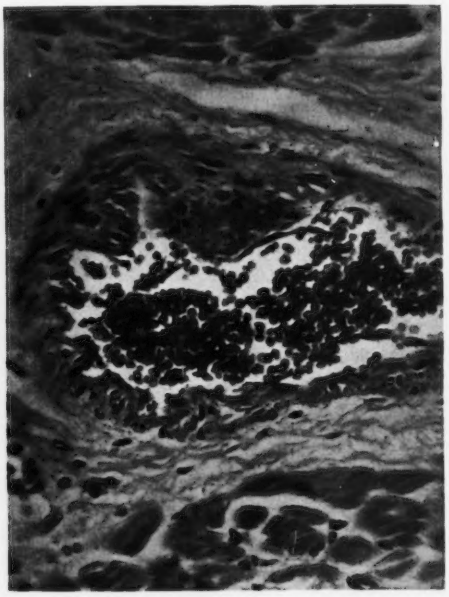

FIG. 3. Section of myocardium of the left ventricle showing an arteriole with focal subintimal fibrinoid necrosis. Hematoxylin and eosin × 264.

of basophilic degeneration. The latter resembled the lesions described by Spencer[41] as "mucoid degeneration" of heart muscle and gave similar histochemical reactions. The significance is unknown, although Bragdon and Levine[42] have observed similar lesions in the myocardium of vitamin E deficient rabbits.

In well-established areas of mucinous edema foci of fibrinoid necrosis appeared. These were manifested by swelling, and disintegration and fusion of collagen into amorphous eosinophilic masses.

Focal endocardial swellings were produced

FIG. 4. Section of myocardium of left ventricle showing subintimal fibrinoid necrosis and fibrinous exudation in a venous sinus. Hematoxylin and eosin × 60.

FIG. 5. Section of myocardium of left ventricle showing an organizing verrucous lesion in a large venous sinus of myocardium. Hematoxylin and eosin × 80.

by a combination of mucoid edema, fibrinous exudate, fibrinoid necrosis and hemorrhage. These resulted in polypoid projections covered by swollen endothelial cells.

Similar endovascular projections were also observed in the thebesian and luminal vessels, in the myocardial venules and arterioles and resembled those described by Holsti[43] as "arteritis verrucosa" and by Siegmund[44] as "fibrinknotchen."

FIG. 6 Section of myocardium of left ventricle demonstrating a diffuse necrotising arteriolitis with marked fragmentation of the myofibrils. Hematoxylin and eosin × 60.

Diffuse necrotizing arteriolitis was noted, but occurred infrequently. An additional, but inconstant, finding was the presence of endothelial cell masses in arterioles and capillaries.

Subacute cases showed cellular infiltration and proliferation. Granulomatous tissue was formed in relationship to the fibrinoid, thrombotic, verrucous and parenchymatous lesions so that these could be observed at various stages of absorption and organization.

There were no specific histopathologic features in this granuloma phase except when it was disturbed by an acute exacerbation. Fresh foci of mucinous edema and fibrinoid necrosis

FIG. 7. Section of myocardium of left ventricle showing organizing of an endovascular thrombotic lesion in the subacute stage. Hematoxylin and eosin × 90.

FIG. 8. A section from the endocardium of left ventricle showing fibroelastosis. Weigert's stain × 400.

were then evident. Altered blood pigment, and chromatin debris were abundant and large histiocytes containing phagocytosed "fibrinoid" material were prominent. Foam cells, eosinophil leukocytes and Anitschkow myocytes were irregularly distributed. Progressive fibrosis resulted in endocardial sclerosis, myocardial fibrosis, and eccentric subintimal connective tissue cushions. These were the characteristics of the chronic stage of the disease.

Wherever endocardial sclerosis occurred it was accompanied by hyperplasia of elastic tissue. These fibroelastic scars occurred as opaque plaques on the endocardium, but occasionally more diffuse thickening of the endocardium was seen.

General Histopathologic Changes

The intima of the aorta showed focal nodular swelling and increased metachromasia in some cases. Similar changes were seen in the subintimal tissues of the vasa vasorum and nodular foci of fibrinoid necrosis were occasionally seen in these regions. Thrombosis in the aorta was not seen in our present series, although it has been reported by Mumme[23] in Löffler's parietal endocarditis.

The lungs showed chronic venous congestion and infarcts, and in several there was thrombosis of the smaller pulmonary vessels. The spleen, liver and kidneys showed the presence of chronic venous congestion. Minute embolization of the glomerular tufts was not uncommon.

DISCUSSION

The recognition of the condition as a type of cardiovascular collagenosis depends upon the demonstration of the degeneration of collagen and its associated ground and cement substances. The early manifestations and subsequent findings in the diffuse collagen diseases have recently been reviewed by several authors, notably Klemperer,[45] Altshuler and Angevine,[46] and Pagel.[47] The earliest change is an increase of the acid mucopolysaccharide of the ground substance manifested morphologically by a mucinous edema and evidence of increased vascular permeability. Precipitation of the acid mucopolysaccharides and swelling and degeneration of the collagen follow. This fibrinoid necrosis is succeeded by inflammatory cell infiltration and hemorrhage or thrombosis, with

subsequent granuloma formation, organization and fibrosis. The nature of these changes differs in detail in each of the diffuse collagen diseases. There are differences in local cytoarchitecture, in the distribution of the lesions and in the presence or absence of epiphenomena such as the valvular vegetations in rheumatic fever and the hematoxylin bodies in disseminated lupus erythematosus. The general design, however, appears constant.

We have demonstrated this sequence of events in the condition under review. The disease begins with a degeneration of the ground substance of the endocardial connective tissues, although other sites may be involved. The chief biochemical substrate of the ground substance of the connective tissues of the parietal endocardium is not known with certainty. It would appear that the location of the target reacting substance in this zone is the crucial factor in determining the specific pathognomonic features of the condition. Although the endocardium in the fetal heart is rich in an embryonic gelatinous reticulum,[48, 49] it disappears later and, as we have shown, chromotropic material in this situation is scanty in normal adult, human hearts.

The lesions seen in acute cases (mucinous edema, increased permeability with serous myocarditis, fibrinous exudation and fibrinoid necrosis) are typical of an acute collagenosis. If these changes are severe and widespread, death usually occurs rapidly as a result of progressive cardiac failure (32.5 per cent in our series). If the changes are severe, but distributed focally, extensive mural thrombosis with granuloma formation and organization ensue. These subacute cases (62.5 per cent in our series) may survive longer. Their course may be punctuated by recurrent acute episodes, any of which may prove fatal. Organized and healed focal endocardial lesions of previous attacks are represented by sclerotic endocardial plaques (5 per cent in our series). In addition, there is evidence to suggest that mild, but more generally distributed endocardial lesions may lead to chronic diffuse endocardial sclerosis through a process of fibrillogenesis and elastic tissue hyperplasia. This may be the explanation of the rare examples of endocardial sclerosis in the adult.[24, 50-53]

Myocardial necrosis and fibrosis are located chiefly in the subendocardial zone and may be anoxic in origin. The source of the anoxia lies in the vascular lesions. In addition, it is possible that the endocardial edema, together with the film of fibrin on the surface endocardium and the endocardium lining the thebesian and luminal vessels may interfere with the blood supply of the endocardium. This may be a factor in the production of anoxia in the inner third of the myocardial wall, although Gregg[54] has warned that the importance of these vessels in the myocardial circulation has not been sufficiently established to warrant statements based on their utilization or nonutilization.

Embolic phenomena arise as a result of the mural thrombus. Another possible source is the narrow-based, imperfectly organized endovascular verrucous lesion.

Morphologic equivalents to the lesions we have described have been frequently reported before. Selye[55, 56] has described an identical process as an integral part of the adaptation syndrome under the term "cardiovascular hyalinosis." Mucinous edema has been reported in the endocardium (auricular, ventricular and valvular) and in Aschoff nodes in rheumatic fever[45] and in the subcutaneous nodules from cases of rheumatoid arthritis; in disseminated lupus erythematosus and occasionally in cysts, bursas and ganglia; in the tissues of patients with diabetes mellitus and myxedema[46]; in the arterial walls in pyridoxine-deficient monkeys[57]; in dissecting aneurysms.[58]

The pathogenesis of fibrinoid necrosis occurrence and distribution has been recently reviewed.[45, 46] It has been previously reported in the condition under review.[24]

Fibrinous exudation has been reported in the endocardium in rheumatic fever[59]; in other collagen diseases, for example disseminated lupus erythematosus,[60] periarteritis nodosa,[47] dermatomyositis,[47] and in this condition.[19]

Verrucous lesions have been described in rheumatic fever[43, 61, 59]; in animals immunized by bacteria[44]; in the vessels of the heart, lung, pancreas and spleen in cases of nonthrombotic endocarditis associated with fever, arthritis

and serositis[62]; in degenerative verrucal endocarditis[63]; in disseminated lupus erythematosus[60]; in allergic syndromes[64]; in disseminated arteriolar and capillary platelet thrombosis[65]; in acronecrosis and tuberculosis.[66]

These are the essential features of the acute phases. The subsequent reactions of endomyocardial necrosis and fibrosis, mural thrombosis, granuloma formation, organization and endocardial sclerosis have been repeatedly and adequately described in the many cases previously recorded in the literature.

TABLE 3.—*Symptoms in 35 Cases with Adequate Clinical Histories*

Complaint	No. of Cases	Per cent
1. Dyspnea	33	95
2. Cough	24	70
3. Swelling of legs	22	62
4. Pain in abdomen	13	38
5. Swelling of abdomen	12	35
6. Pain in chest	11	32
7. Hemoptysis	11	32
8. Anorexia	8	22
9. Swelling of face	8	22
10. Nausea	7	19
11. Vomiting	6	16
12. Bouts of dyspnea	5	14
13. Loss of weight	4	11
14. Swelling of hands	3	8
15. Palpitations	2	5
16. Diarrhea	1	3

CLINICAL PRESENTATION

The clinical presentation was that of a rapidly fatal condition, the average duration being about six months with a range of less than a month to three years.

The commonest initial manifestation was progressive exertional dyspnea (68 per cent). In two cases the onset of the breathlessness was sudden and suggested pulmonary edema. Pulmonary infarction or embolism appeared to initiate the illness in two cases. Sudden breathlessness, pain in the chest and hemoptysis characterized this group. Pain in the chest and subsequent dyspnea (two cases), cough and subsequent dyspnea (two cases) hemoptysis (one case) and syncopal attacks, coma and hemiplegia (one case) were the first indications of the illness in the remainder.

Dyspnea figured prominently in the histories of 95 per cent of the cases. In many, swelling of the legs, abdomen and occasionally the face and hands appeared soon after the dyspnea: the development of edema averaged three weeks, after the onset of dyspnea in the groups classified as acute or subacute. Edema followed exertional dyspnea by one and two years in the two cases classified as chronic. Hemoptysis tended to occur later in the illness, although it could be the first indication. The average interval between the onset of dyspnea and hemoptysis was seven weeks with a range of a few days to three months.

TABLE 4.—*Physical Findings in 35 Cases*

Physical Findings	No. of Cases	Per cent
Dyspnea	35	97
Raised jugular venous pressure	31	84
Tachycardia > 100 per minute	30	81
Pulmonary congestion	30	81
Tachypnea > 24 per minutes	29	78
Edema of legs	26	70
Cardiomegaly	25	68
Hepatomegaly	25	68
Orthopnea	23	62
Systolic murmur	18	49
Gallop rhythm	16	43
Pyrexia	15	40
Ascites	15	40
Pleural effusion	15	40
Edema of sacrum	12	32
Edema of abdominal wall	12	32
Edema of face	7	19
Hemiplegia	4	11
Psychic disturbances	3	8
Diastolic murmur	3	8
Arrhythmia	3	8
Edema of hands	3	8

An average duration of two months, ranging from a few days to 12 months preceded the admission to hospital in the acute and subacute types. The complaints that developed during this relatively short time are listed in table 3.

Many were in congestive cardiac failure on admission to hospital. This was absent in a few patients who were first seen in peripheral circulatory failure and died soon afterwards. The physical findings are shown in table 4.

Pyrexia up to 102 F. occurred in 81 per cent

and varied from an occasional solitary elevation to bouts which lasted from a few days to weeks. Deterioration of the patients' condition was noted during these pyrexial periods. A tachycardia from 100 to 150 was present in 81 per cent, tachypnea was noted in 78 per cent.

A blood pressure estimation was available in 24 patients. The average systolic, diastolic and pulse pressures were 116, 83 and 32 mm. Hg, respectively. The diastolic pressure exceeded 100 mm. Hg in six cases and in an equal number the systolic pressure was below 100 mm. Hg.

A radiologic examination of the chest was carried out in 20 cases. The cardiac silhouette was considered to be enlarged in 19 of these, the majority at the initial examination and in two cases during subsequent examinations. The cardiac enlargement was generalized with the exception of one case with hypertension which showed marked enlargement of the left ventricle and left auricle. A characteristic feature of the group with marked enlargement was the slight movement of the heart borders. A gross pericardial effusion was diagnosed in one case and in others it may have been partly responsible for the enlargement and diminished movements of the heart.

A right-sided pleural effusion was present in nine and a left-sided pleural effusion in 10 cases. A mottled loss of translucency in the hilar regions ("bats-wing" appearance) with clear peripheral lung fields was present in three cases and varied in intensity with the increase or decrease of the heart failure. The lesser fissure of the right lung was prominent in seven, the pulmonary arteries in three, congestion of the lung bases in six, and radiologic evidence of infarction in two cases.

From one to seven electrocardiograms were available in 17 cases. A sinus rhythm was present in 13 cases. Four cases showed ventricular extrasystoles. In two of these cases a bigeminal rhythm resulted. One subject had a supraventricular tachycardia probably of nodal origin. The P-R interval exceeded 0.21 second, in two cases, while one example of a left and another of a right bundle branch block pattern were seen. Eight cases showed a prolongation of the Q-T time. Abnormalities of the P wave occurred in six cases, in three of which the amplitude exceeded 2.5 mm. in lead II. The P waves were markedly notched in one case, flat topped in another and had a duration of 0.14 second in two cases. One electrocardiogram showed RS-T segment elevation in the standard leads. All the remaining cases showed depression of the RS-T or flat or inverted T waves.

The electrocardiogram was abnormal in every case. The abnormalities found were chiefly present in the RS-T segments and T waves. Only one case showed evidence of RS-T segment elevation and an organizing fibrinous pericarditis was present at autopsy. Nine cases showed depression of the RS-T segments which may have been related to the predominant subendocardial damage found at postmortem examination. In some, this change may have been produced by digitalis administration. The prolongation of the Q-T time is in keeping with the generalized myocardial damage found at autopsy. The P-wave changes may have been due to the pathologically observed involvement of the auricles or dilatation of the auricle with failure of the left ventricle.[67]

Albumin was present in the urine of 21 of 30 patients in whom the urine was examined. Microscopic examination showed pus cells in three, a few squamous cells, granular and hyaline casts in two, and the latter plus red blood cells in two cases. The Wassermann test was negative in 11 cases, strongly positive in one and doubtful in another case. The blood urea nitrogen was estimated in eight cases. It was raised in all with an average of 70 mg. per 100 ml. blood and a range from 40 to 144. One case showed a progressive increase from 49 to 144 mg. per 100 ml. blood while another showed a drop to normal limits with serial estimations. From one to five blood counts were available in 13 cases. Seven of these were considered to show slight to moderate anemia, five were normal and one case showed an initial anemia which subsequently become normal. A white blood cell count had been done in 12 cases, seven showing a leukocytosis (10,700 to 29,000 per cu.mm.), one a leukocytosis and subsequently a leukopenia, one a leukocytosis which

subsequently became normal and in one case the count was normal throughout the illness. A marked absolute eosinophilia was present in one case and moderately elevated in another. The blood sedimentation rate was raised in the three patients on whom the estimation was made. The blood proteins were low, less than 5.6 Gm. per 100 ml. blood in four of the eight patients examined. The blood albumin was low, less than 3.4 Gm. per 100 ml. blood in five and normal in two cases. The globulin was raised in one, reduced in another and within normal limits in the remainder. The albumin-globulin ratio was below 1.5: 1 in five cases. This was due to an absolute increase in the globulin in one case and a disproportionately larger decrease in albumin than globulin in the others. A normal decrease in the blood eosinophil count following the injection of adrenocorticotropic hormone (ACTH) was found in one case.

The broad outline of the clinical picture is the absence of the common etiologic factors usually found in heart failure, the early onset of congestive cardiac failure following progressive exertional dyspnea and the rapidly fatal course of the illness.

The physical and laboratory findings generally differed in no way from those commonly associated with a severe and rapidly progressive congestive cardiac failure. However, the dyspnea, tachycardia, hepatomegaly and serous cavity effusions appeared in many to be disproportionately increased in comparison with the degree of congestive cardiac failure. Eosinophilia was inconstant.

Summary

1. Forty cases of endomyocardial necrosis and fibrosis with parietal endocardial thrombosis have been studied.

2. Histopathologic evidence is produced indicating that the condition belongs to the group of diffuse collagen diseases.

3. The clinical picture and pathologic findings are sufficiently distinctive to warrant the recognition of this condition as a specific disease entity for which we have suggested the name of cardiovascular collagenosis with parietal endocardial thrombosis.

Sumario Español

Cuarenta casos de trombosis del endocardio fueron seleccionados de un total de 9,500 autopsias practicadas durante 1936 a 1951. Envolvimiento focal diseminado del tejido conectivo en todo el organismo y particularmente en el corazón fue demostrado. Aunque los hallazgos histopatológicos fueron muy similares a los encontrados en enfermedades difusas de tejidos colágeno, no demostraron las características de las lesiones en fiebre reumática, periarteritis nodosa, lupus eritematoso o escleroderma difusa. El síndrome clínico de decompensación cardíaca rápidamente progresiva con los hallazgos patológicos fueron suficientemente distintivos para considerar esta condición como una colagenosis cardiovascular con trombosis parietal del endocardio. Una condición similar ha sido descrita bajo una variedad de nombres y ha parecido constituir una gran proporción de los casos de llamada hipertrofia idiopática o miocarditis del corazón.

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The Weight of the Heart and Its Chambers in Hypertensive Cardiovascular Disease with and without Failure

By RUSSELL S. JONES, M.D.

The myocardial weights of the different cardiac chambers were determined in 130 cases of hypertensive cardiovascular disease, both with and without failure. The left ventricle hypertrophies before and continues to hypertrophy after the advent of congestive failure. The right ventricle and both auricles hypertrophy only after failure develops. In correlating the ventricular work with its muscle mass, the left ventricle apparently performs twice as much work per gram as the right ventricle. Several possible explanations for this apparent greater efficiency of the left ventricle are presented. The changes in chamber weights are discussed in relation to concepts of congestive failure.

MORE is known of the physiology of the heart than of any other organ, primarily because of the knowledge of mechanical principles and the development of the sphygmomanometer, roentgenography, electrocardiography and cardiac catheterization. It is, therefore, surprising that a further means of understanding cardiac function has been neglected, that is, the determination of the different chamber weights. From such information the degree and sequence of hypertrophy of the different chambers might be established. Accurate methods for determining the weights of the myocardium of the different chambers were devised by Müller[1] in 1883, Wideroe[2] in 1911, and Lewis[3] in 1913. Lewis, basing his study upon 23 controls, 46 cases of valvular disease and 27 of "nephritis," observed that (a) elevated blood pressure was the most potent factor in producing preponderance of the left ventricle, (b) general and uniform hypertrophy of both ventricles is frequent in renal disease and (c) the ventricles are heavier in mild nephritis than with marked contraction of the kidneys. He advised that "before we can consider our knowledge of hypertrophy in relation to valvular or renal disease to be complete, the number of hypertrophied hearts studied must be multiplied." This has not been done, although there are correlations of electrocardiographic axis-deviation with ventricular weights[4] and of pulmonary diseases with weights of the chambers.[5, 6]

It is the purpose of this paper to: (a) present a simple and reliable technic for determining myocardial hypertrophy of the different chambers, (b) indicate the degree and sequence of hypertrophy of the different cardiac chambers in compensated and decompensated hypertensive cardiovascular disease, (c) correlate these changes with concepts of congestive failure and (d) compare the work per gram of myocardium of the two ventricles.

METHODS AND MATERIALS

Technic of Dissecting the Heart

After routine weighing of fresh or formalin-fixed hearts, the myocardium is freed of epicardial fat, extramyocardial coronary arteries, cardiac valves and the attached portions of aorta, pulmonary artery, pulmonary veins, venae cavae and any tissue or mass of any appreciable weight which does not represent myocardium. This leaves only the myocardium of the cardiac chambers. The chambers are then divided into four segments: the left ventricle, the interventricular septum, the right ventricle, and the two auricles. The illustrations (fig. 1) demonstrate how this dissection may be performed most easily. The right ventricle is detached from the interventricular septum by cutting through the ventricular wall close to the septum and in a plane parallel to the septum. One follows closely along the interventricular wall at the pulmonary valve and finally, the right ventricular wall is completely freed

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by detaching it from the tricuspid ring. The left ventricular wall is removed in a similar manner:

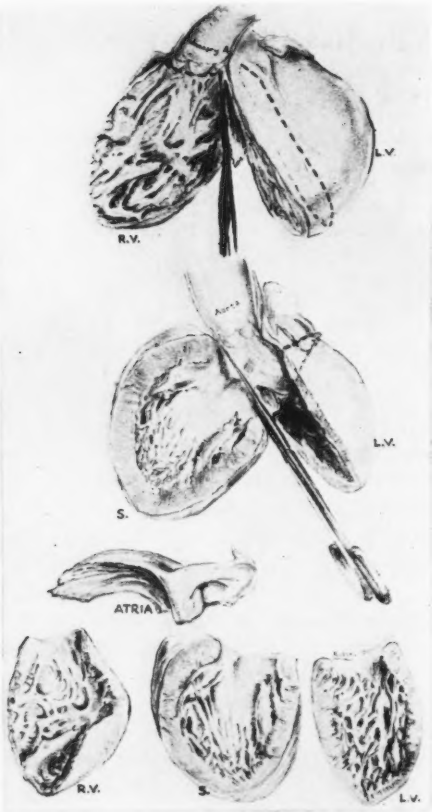

FIG. 1. The Technic of Separating the Myocardium of the Different Cardiac Chambers. Epicardial fat and larger extramyocardial coronary vessels are removed. The right ventricle is exposed (top figure) by incising close to the interventricular septum. Its lateral wall (R. V.) is then detached by cutting along the juncture with the auricle (site of scissors) and at the base of the pulmonary artery. The middle figure shows the removal of the interventricular septum (S.) after the left ventricular lateral wall (L. V.) has been detached by incising close to the septum and along the dotted line which denotes the auriculoventricular junction. Both auricles together are then separated from the pulmonary artery, aorta, valves and any pericardium or other nonmyocardial tissue. The bottom figure shows the four segments thus obtained.

incisions are made close to and parallel to the septum and as perpendicular as possible to the overlying epicardial surface (so that the inner endocardialized portion of the septum equals the thickness of its outer sectioned portion); the sectioning is extended across the base of aortic valve and then the lateral wall of left ventricle is completely detached by removal from the left auricle at the mitral ring. The interventricular septum is the only remaining myocardium attached to the auricles, aorta and pulmonary artery. The septum is freed by cutting through its membranous portion at the base of aortic and pulmonary valves. This leaves the combined auricles to be detached from aorta and pulmonary artery, their valves, portions of parietal pericardium, epicardial fat and as much as possible of the fat in the outer part of the interauricular septum. The four segments of myocardium are now accurately weighed, the sum of their weights representing the "true" myocardial weight.

Discussion of the technic. It is believed that the above technic affords a favorable balance between simplicity and accuracy. Since this technic, like previous ones, differs in various aspects, some explanation for the selection of the above methods of dividing each of the different myocardial segments should be given. After initial studies it was observed that the auricles were difficult to divide accurately at the interauricular septum and that they are usually of equal weight. Therefore, in subsequent dissections the two auricles were left attached and weighed as a single segment. Division of the septum into its left and right ventricular components cannot be carried out with ease or accuracy. Initial studies of dividing the septum by serial transverse sections, then separating each of the sections at the juncture of "scroll" muscles indicated that the ratio of the right to left ventricular septal components equalled that of the nonseptal components, that is, 1 to 2. Accurate separation of the left ventricular wall from the septum is obviously difficult, since the septal wall of the left ventricular wall is concave. Nevertheless, there was an unexpected uniformity and equality of the interventricular septum to the left ventricular lateral wall weights.

The lateral wall of the right ventricle can be most accurately determined by this method. Its detachment from the relatively flat interventricular septum and adjoining structures is readily accomplished, a few portions of trabeculae carneae representing the only points of uncertainty in sectioning. The right ventricle is also usually free of infarction or fibrosis but may show some infiltration of adipose tissue.

Besides the above technical errors there are other sources of inaccuracy. These are related to the presence in the myocardium of collagen, amyloid, fat, edema fluid, "swelling of ground substance," and leukocytes. Considerable fluid drains from a sectioned heart over a period of several hours. Although the reduction in weight through fluid loss is probably of the same degree in all parts of the myocardium, a 20 per cent loss can occur over a 12-hour period. Considerable increase in weight is possible from

thrombi or blood clots clinging to the heart or from fluid clinging to the numerous crevices and surfaces in a recently washed heart.

The weights of the ventricular walls are of prime importance in this study and are accurate within the technical limitation of this method.

Classification of Material

Six hundred eight unselected hearts of children and adults were studied. Of this total group 110 patients were free of cardiovascular disease, emaciation, significant anemia, chronic pulmonary disease, and renal disease and were utilized as controls. Eighty-five of these were adults. One hundred thirty hearts were from patients with hypertensive cardiovascular disease and form the basis of this report. Eight cases, grouped separately for comparative purposes, had either fluctuating hypertension or a history of hypertension but none recently. Two hundred ninety cases were grouped in various other categories such as thoracic disease, congenital anomalies, valvular lesions, coronary thromboses and mixed. The remaining 70 cases had inadequate clinical records and were discarded.

For comparative purposes cases of fluctuating hypertension and cases with previous hypertension but none prior to death are listed, while the cases with hypertensive cardiovascular disease are subdivided as follows:

1. Compensated: (a) Death from noncardiovascular causes. (b) Death from cerebrovascular accidents. (c) Previous cerebrovascular accidents then death from noncardiovascular causes. (d) Death in uremia.

2. Decompensated: (a) For a few weeks. (b) Over a few weeks and up to one year. (c) From one to three years. (d) Over three years.

The diagnosis of hypertension was based upon a "fixed" diastolic blood pressure over 100 mm. and a systolic pressure over 150 mm. Hg prior to failure in patients without significant cardiac valvular lesions, anemia, chronic pulmonary changes, or other diseases which might give rise to cardiac hypertrophy. The diagnosis of cardiac failure was based upon the symptoms of orthopnea, paroxysmal dyspnea, and exertional dyspnea, and the signs of pulmonary edema, hepatomegaly, ascites, and peripheral edema.

It was not possible accurately to distinguish left ventricle failure alone from that combined with right ventricular failure. Therefore, "decompensation" was used to denote irrefutable evidences of failure as indicated by combinations of the above clinical findings. The onset of hypertension usually was uncertain; therefore, no classification in regard to the duration of hypertension was deemed valid. The existence of essential hypertension was substantiated by microscopic evidence of visceral arteriolosclerosis.

Observations

Control (Normal) Values

In the adult the myocardial weight after removal of fat, great vessels and clots is approximately 200 Gm. The relative weights of the different chambers are quite uniform and closely approximate the easily recalled ratios of 2:2:1:1 for the left ventricular lateral wall (L.V.), the interventricular septum (Sept.), the right ventricular lateral wall (R.V.), and both auricles (Aur.), respectively. The relationships of the chamber weights in the adult may be presented by comparing the actual weights, the percentages, and the numerical ratios as follows:

	Myocardial Wt.	L. V.	Sept.	R. V.	Aur.	L/R
Grams....	200	66	66	33	34	2.0
Per cent..		33.3	33.3	16	17	
Ratio		2	2	1	1	

Early interest in concentric and eccentric hypertrophy of the heart was reflected in the emphasis placed upon the left to right ventricular (L/R) ratio. In Lewis's[3] controls this ratio ranged from 1.57 to 2.18, averaging 1.8. Lewis's dissection resulted in a relatively small septal bulk which was not considered in the calculation of the ratio. Müller[1] divided the septal weight by calculation into right and left portions and added these to the respective right and left ventricular weights to arrive at a right to left (R/L) ventricular ratio of .552. Lewis's L/R and Müller's R/L ratios are almost identical reciprocals of one another. The L/R ratio obtained by Hermann and Wilson[4] in 16 controls averaged 1.74. They divided the formalin-fixed heart at the juncture of the scroll muscles in the septum and thus avoided any separate septal weight.

In the present study the estimation of the ventricular ratio is based, like Müller's, upon the calculation of the weight of the left and right ventricular portions of the septum. In a preliminary group of 15 hearts it was found that the ratio of the right to left septal portions was approximately the same as the ratio of the left and right lateral walls. Estimation of the

L/R value could be based upon the ratio of the sums of the septal plus lateral wall portions of the respective ventricles:

$$\frac{L}{R} = \frac{L.V. + \left(\frac{L.V.}{R.V. + L.V.} \times Sept.\right)}{R.V. + \left(\frac{R.V.}{R.V. + L.V.} \times Sept.\right)}$$

The resulting L/R value actually would be the same as if the lateral wall values alone had been used. Since the weight of right lateral wall value is determined with the greatest accuracy and the septum and left lateral ventricular wall, in contrast, are difficult to divide, it was decided to average the weights of the septum and left lateral wall and then divide by the right lateral ventricular weight:

$$\frac{L}{R} = \frac{Sept. + L.V.}{2R.V.}$$

This calculation, however, fails to consider the changing ratio of right and left septal portions in hypertrophy. For example, a twofold right ventricular hypertrophy should give an L/R value of 1.0 but by the last formula the L/R would be 1.17. A twofold increase in the left ventricular weight should have an L/R of 4.0 but by the formula yields 3.67. By graphically charting a number of such relationships the following corrected value, $\left(\frac{L}{R}\right)_c$, is derived.

$$\left(\frac{L}{R}\right)_c = 1.19\,\frac{L}{R} - 0.37$$

The L/R of 2.0 used in this report is a convenient approximation, the actual average for the adult controls being 1.92 with a range of 1.36 to 2.43. These extreme ranges are unusual but are utilized for completeness since control series in previous reports included cases with similar diseases. The few low L/R ratios occurred in the patients with metastatic carcinoma and a low "true" myocardial weight but without marked weight loss. The high ratio of 2.43 occurred in a patient dying from traumatic injuries but also having portal cirrhosis. The need for further study of the cardiac function in different diseases is suggested by this variation of the L/R ratio and total myocardial weight.

The L/R values alone cannot indicate the entire relationship of ventricular weights. If both ventricles were hypertrophied or atrophied to the same degree the ratio would be the same as before. To give a more complete picture the various chamber weights may be tabulated and graphically charted or the L/R value may be supplemented by the ratio of observed to expected myocardial weights. In the latter method, comparison to the expected weights would give a ratio of 4:2 instead of the usual 2:1 (or 2.0). In this paper these data have been tabulated (table 1) as well as graphically charted (fig. 2).

Values in Hypertensive Cardiovascular Disease

A complete analysis of the sequence and degrees of hypertrophy in the different cardiac chambers has not been possible for two major reasons: (a) the onset of hypertension is rarely known, hence, the effect of duration of hypertension upon degree of left ventricular hypertrophy cannot be evaluated; (b) clear and unequivocal evidences of left ventricular failure without right ventricular failure are usually not obtainable from the clinical or hospital records, hence, "decompensation" in this paper is applied to all cases with definite evidences of failure. However, the data presented in table 1 and figure 2 do indicate the effect of failure as well as the duration of failure upon the relative chamber weights.

In the compensated phase the left ventricle hypertrophies while the right ventricular and combined auricular weights remain unchanged. This has been termed "eccentric" hypertrophy in the older literature. With the onset of failure the left ventricular weights continue to increase but now the right ventricle hypertrophies along with a parallel increase in the combined auricular weights. Finally, the hypertrophy becomes "concentric." Expressed as ventricular ratios, the L/R is high in compensated hypertrophy, but approaches normal in protracted failure. The average left ventricular and septal weights in the seven cases with failure for over three years (group X, fig. 2) was less than that of group IX with failure

from 1 to 3 years. The reason for this is uncertain and the small number of cases makes one hesitate to consider as significant such factors as the older average age, the degree of hypertension, the severity of failure and the effects of digitalis and diuretics. The problem of partial atrophy following a marked hypertrophy of the heart awaits further investigation.

In the present study, careful examination of the coronary arteries was performed. It was interesting to note that marked myocardial hypertrophy did not occur when the coronary arteries were markedly narrowed by atherosclerosis. This is contrary to the belief of some[7,13] that local myocardial hypoxia resulting from coronary arteriosclerosis may induce hypertrophy of the involved area. It is probable, however, that coronary arteriosclerosis may influence the myocardial weights in many ways such as (a) by limiting the degree of myocardial hypertrophy in severe hypertension, (b) by leading to progressive ischemic effects on an overtaxed, hypertrophied myocardium, and (c) by shortening the patient's life and hence interval of time in which hypertrophy could occur.

In the "compensated" group, the cases dying in uremia but free of significant failure showed the most marked hypertrophy of the septum

TABLE 1.—*Myocardial Weights in Hypertensive Cases with and without Failure*

	Number of Cases	Age Range	Av. Age	Av. Gross Wt. of Heart (Gm.)	Av. Myocardial Wt. (Gm.)	Av. L.V. Wt. (Gm.)	Av. Sept. Wt. (Gm.)	Av. R.V. Wt. (Gm.)	Av. Aur. Wt. (Gm.)	L/R
Cases Without Failure										
I. History of hypertension but none recently	3	51–67	58	286	208	61	80	30	36	2.47
II. Fluctuating hypertension	5	35–75	59	332	231	90	81	33	31	2.59
III. Hypertensives without failure dying of noncardiovascular and nonrenal lesions	19	27–78	54	319	246	88	87	34	36	2.57
IV. Death from cerebrovascular lesions	45	37–78	59	384	298	111	106	36	40	3.01
V. Previous cerebrovascular accidents, then death from noncardiovascular causes	2	66–81	—	360	280	100	109	34	36	3.07
VI. Death in uremia without significant failure	7	42–58	50	425	352	141	129	37	43	3.64
Cases With Failure										
VII. Failure for a few weeks only	4	34–49	42	421	374	151	128	47	48	2.97
VIII. Failure over a few weeks and up to one year	35	29–82	57	414	349	126	124	51	52	2.58
IX. Failure from 1 to 3 years	11	34–79	58	516	449	157	146	74	69	2.28
X. Failure 3 years or more	7	56–72	65	428	364	123	116	67	58	1.89

L. V.—Left Ventricle, lateral wall.
Sept.—Interventricular septum.
R. V.—Right Ventricle, lateral wall.
Aur.—Both auricles.
L/R—Ratio of left to right ventricular weights.

and left ventricle with only a mild increase in the auricular and right ventricular weights. The hypertension was not necessarily more severe in these cases but the fluid and electrolyte disturbances may have led to hypervolemia and hemodynamic alterations.

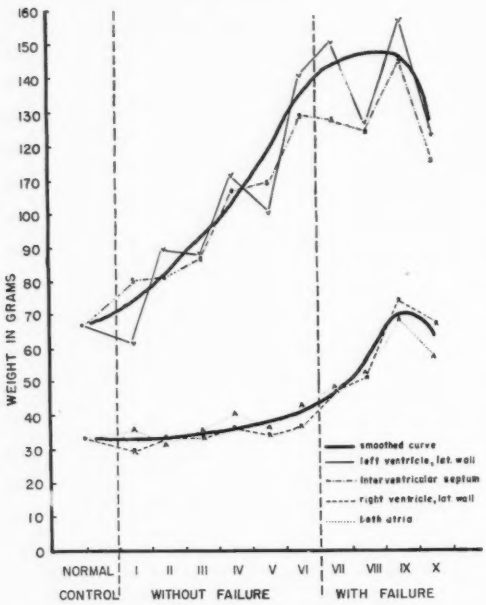

FIG. 2. The Effect of Hypertension and of Hypertension with Failure upon the Mass of the Different Cardiac Chambers. The data and groups of cases in table 1 are graphically presented. Groups I through VI are not arranged as to duration of hypertension, while groups VII to X are presented as to duration of failure. The smooth curves, however, suggest that the left ventricular and septal weights increase before and after failure, while the right ventricular and combined auricular weights increase only after failure ensues. The general equality of septal with lateral left ventricular wall weights and of both auricles with lateral right ventricular wall weights is seen.

DISCUSSION

Relation of Myocardial Bulk to Work Performed

In the absence of local infiltrations or of disease, the myocardial bulk of any chamber should be proportional to work performed by that chamber. This view finds support in the following observations: (a) the relatively constant ratio of heart weight to body weight with growth and maturity, (b) the fairly constant L/R values for all ages after infancy,[1] (c) similarity of L/R values in different species of mammals,[8] (d) hypertrophy from increased work of a chamber, as from valvular lesions and hypertension, (e) hypertrophy of other forms of muscle from increased work, as skeletal muscle in exercise and smooth muscle in obstructed hollow organs. It would appear reasonable to conclude that increased work leads either directly or indirectly to hypertrophy. This is disputed. An even more uncertain aspect is the means through which such mechanical work may lead to growth of the myocardium, the following factors having been suggested: intracardiac neurologic reflexes, temporary stretch causing nutritional effects, injury or "toxic" products therefrom, impaired blood flow as well as increased blood flow.[9] Some of these have been proposed as operating, per se, and not necessarily from mechanical factors. It is obvious that the cause and mechanism of myocardial hypertrophy are poorly understood, and that the various suggested biochemical or physiologic factors have not clarified the problem. Some idea of the relationship of work performed per weight of the myocardium may be gained from a discussion of the factors involved in the work of the heart and from the data presented in this paper.

The heart performs work in two ways, first by ejecting a certain volume of blood against resistance or pressure (static factor) and secondly by imparting a certain velocity to this ejected blood (kinetic factor). The work (W) of a ventricle is the sum of these two components and may be expressed by the following formula[9, 10]:

$$W = QR + \frac{MV^2}{2g} \; Kg.\ M.\ per\ second$$

in which W = work in kilogram meters per second; Q = liters of blood expelled per second; R = mean blood pressure in terms of meters of blood; M = mass of blood ejected in kilograms per second; V = velocity at which blood is ejected in meters per second; and g = gravity constant (9.81 meters per second^2).

The static component of ventricular work (work against resistance, QR) is the product of

cardiac output and mean systolic ejection pressure. This use of mean pressure may yield a 10 to 20 per cent error[9] since blood is ejected against a variable and not a constant pressure. The kinetic component, $\frac{MV^2}{2g}$, is not easily assessed in man although efforts have been made to do so.[9, 11, 12, 13]

Relation of Left Ventricular Weight to Work Performed

Right ventricular weights could not be correlated with work of this chamber since cardiac catheterization was not performed in any of these patients. In figure 3 an attempt has been made to correlate the weight of the left ventricle with the work performed by this chamber. The total left ventricular weights (lateral wall and septal portions) per square meter of body surface are plotted against the mean arterial pressures. Only those cases with repeated blood pressure recordings were utilized; the seventy-eight plotted cases are equally divided between those without failure (circles) and those with failure (crosses). The dotted line drawn near the mid-area has the approximate value of $W = 1.06P - 46$, in which W represents the left ventricle in grams per square meter body surface and P, the mean arterial pressure. The failure cases are equally distributed on either side of the dotted line while the greater proportion of the compensated cases occur below the line. The relation of weight to work performed as presented in figure 3 should be regarded more as a guide for future investigations than as an accurate analysis since the work cannot be expressed by the blood pressure alone without knowledge of the output. Also, the blood pressure in cases with failure will be lower than in compensation, and the blood pressure in cerebrovascular accidents may have been augmented by increased intracranial pressure. The probable straight-line relationship in figure 3 does suggest, however, that within wide variations the increasing bulk of the left ventricular myocardium is associated with increased work as manifested by increased blood pressure.

There were two cases (only one of which is plotted in figure 3) of irrefutable hypertension with ensuing failure for over 7 and 10 years in which the total left ventricular bulk was of less than normal value. The right ventricle weighed more than the left. This small left ventricular weight is not easily explained, but several possibilities may be mentioned: atrophy following previous hypertrophy, adaptation of body to diminished blood supply, assumption of left ventricular work (such as increased filling pressure) by the right ventricle. One of these patients was 68, the other 72 years of age, but plotting all cases in figure 3 against age did not show a more significant correlation. Separate plotting of all cases of uremia, cerebrovascular accidents, and marked coronary atherosclerosis also failed to show a more significant relationship.

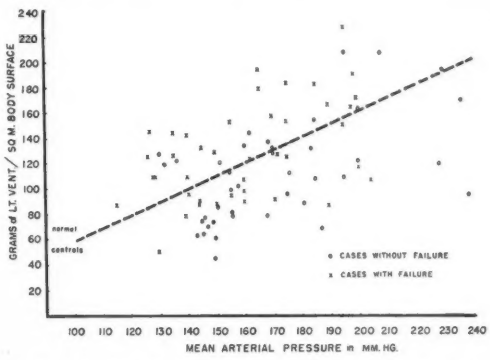

FIG. 3. The Relation of Left Ventricular Muscle Mass to Systemic Blood Pressure. The mean arterial pressure is correlated with the muscle mass of the left ventricle per square meter of body surface. Since the cardiac output was not known in these cases, the actual work of the left ventricle could not be determined. The dotted line drawn centrally indicates the general trend for muscle mass to increase with increased blood pressure.

The Apparent Greater Efficiency of the Left as Compared with the Right Ventricle

Comparison of the two ventricles discloses difference in their work per gram of myocardium, the right ventricle appearing less efficient than the left. Since the difference in the work of the two ventricles is almost entirely proportional to the differences in their pressures, it is usually considered that the right ventricle performs only one-sixth of the work

of the left ventricle[11] although this may be only a rough approximation.[13] Actual measurement of the work of the two ventricles suggests a less marked difference. Dexter[14] found the work of the right ventricle in eight normal resting controls ranged from 0.64 to 1.10 Kg.M. per minute per square meter, with an average of 0.89, but considered Riley's[15] somewhat lower values for three normal patients as a more accurate basal figure. Left ventricular work is approximately 4.5 to 6.0 Kg.M. per minute[10] or 2.5 to 3.5 Kg.M. per minute per square meter. Thus, the work of the left ventricle is at least three and maybe six times that of the right ventricle while the left ventricle only weighs twice as much as the right.

When using the more conservative values for the comparison of the work of the ventricles we obtain:

$$\frac{L.V.\ Work}{L.V.\ Weight} \Big/ \frac{R.V.\ Work}{R.V.\ Weight} = \frac{3.0}{110} \Big/ \frac{0.7}{55} = 2.14$$

The left ventricular myocardium performs at least twice as much work per gram as the right ventricular myocardium. There are several possible explanations for the seeming greater relative efficiency of the left ventricle: errors in estimation of ventricular work, errors in dividing the myocardium between right and left ventricles, the relation of wall thickness and ventricular volume to force of contracture.

The greater efficiency of the left ventricle cannot be explained by the kinetic component of work. The kinetic factor is negligible at rest and is generally disregarded in the estimation of cardiac work. Only when there is a marked increase in the cardiac output and hence, the velocity of blood, does the kinetic factor reach significant proportions necessitating its calculation in the work of the heart. In strenuous exercise the kinetic factor may be in excess of 10 per cent of the total work performed and in violent activity it may exceed the static factor.[10] This disproportion is to be expected since the kinetic factor increases as the cube of the output while the static factor increases in direct proportion to the output. The kinetic factor on the two sides is about equal since the velocity of blood in the pulmonary artery and aorta is the same, the latter being determined by similar cross-sections of the two arteries and equal volume output of the two ventricles.

The division of the septum into right and left portions may have been erroneous in all reported methods since Müller.[1] If the entire septum is considered as left ventricle the above ratio of work per gram of myocardium is approximately 1.0.

$$\frac{L.V.\ Work}{L.V.\ Weight} \Big/ \frac{R.V.\ Work}{R.V.\ Weight} = \frac{3.0}{132} \Big/ \frac{0.7}{33}$$

Finally, there is the basic problem of muscle function with such well-known aspects as the stretch of the muscle fibers, the diastolic and systolic volumes, the contracture distance, and the wall thickness. The observations that the energy of contraction of voluntary muscle is proportional to its stretch[16, 17] were applied to the heart by Starling to explain the wide adaptability of this organ to increased load. The "law of the heart" (cardiac output as a function of diastolic volume) was subsequently amplified[18, 19, 20] and related to the work of the heart, the energy of contraction being proportional to the diastolic ventricular volume, hence, to the length of the muscle fibers. It is generally interpreted that the myocardial fibers do more work by contracting the entire distance over which they have been stretched by the greater diastolic volume, but the actual contracture distance was not regarded by Starling and his associates[19, 20] as a significant factor. They contended that systolic volume was unrelated to oxygen consumption of the heart and that the unimpaired heart responded to increased work by greater diastolic as well as greater systolic volume. This was true whether the work increase resulted from elevated arterial resistance or increased output. While these conditions occurred in the heart in "good condition" in the heart-lung preparation, it was further contended that "as the heart tires it has to dilate continuously in order to maintain its mechanical performance constant." Thus, both the intact and "tiring" heart are aided in work performance through dilatation.

Gesell[21] believed these observations by Starling and associates required broader interpretation, especially in regard to the surface-volume factor. If the ventricle is considered

roughly spherical then the volume of the dilating chamber increases more rapidly than the surface (surface = $4\pi r^2$; volume = $\frac{4}{3}\pi r^3$). The greater the ventricular volume, the greater will be the output per unit length of muscle shortening. Or, a constant output may be maintained by ventricular dilatation and a shorter contracture-distance of the muscle fibers. Applied to the observations of Starling as cited above, we will expect a difference in the contracture distance depending upon which component of static work is augmented; increase in work-against-resistance is accompanied by a shortened contracture distance, while work of the same magnitude due to increased output will be associated with a relatively greater contracture distance. And the "tiring" heart of the heart-lung preparation performs the same work by chamber dilatation and by reduction of contracture distance.

The observations of subsequent investigators[22, 23, 24] have indicated that the heart expends more energy in performing increased work due to augmented arterial resistance than it does in performing equivalent work from greater output. Also, dilatation of the heart is not accompanied by increased mechanical efficiency, which remains about the same with increased venous inflow and is diminished with augmented resistance-load.[24] This correlates well with the changes in contracture-distance of the muscle fibers. It is also possible that increased resistance load or afterload requires more energy in raising the interventricular pressure, the mechanical efficiency thereby being reduced.[24] Further elucidation of the significance of the contracture distance, the initial tension and initial length of muscle fibers is needed. The isolated analysis of a physiologic phenomenon, such as by the heart-lung preparation, does not reconstruct the normal function[25]; the innervated heart, for example, does not show the same diminution of mechanical efficiency for increased resistance-load as the isolated heart.

The apparent greater efficiency of the left as compared to the right ventricle may have some relationship to a difference in their surface-volume or contracture-distance factor. Since the output of the two ventricles is the same, a difference in their contracture distances must be related to a difference in systolic volume, but the estimated diastolic volume of the two ventricles is approximately the same.[9] If, however, the left ventricle has the smaller volume, as one might interpret from the gross appearance at autopsy, then the average contracture distance of its fibers would be greater, and presumably more effective in performance of work. At the same time this would imply a greater "reserve" of the right ventricle[26] not only as a work per gram basis but also since its contracture distance will change less with increased work or with failure.

There is a further aspect which might have some bearing on the relative efficiencies of the two ventricles. In a thin-walled spherical viscus, the true wall thickness varies inversely with the square of the radius, while the "effective wall thickness" of Brody and Quigley,[27] based upon the number of elastic fibrils in 1 cm. of unstretched wall, is proportional to the first power of the radius. If this concept may be applied to a thick-walled, nonspherical contractile ventricle, the ratio of "effective wall thickness" of the ventricles at equal diastolic volumes would be the same as the ratio of the true wall thickness at the "unstretched" systolic values. If the ratio of "effective thickness" to actual thickness were to be increased 2.14 times, thereby accounting for the greater relative efficiency of the left ventricle, the chamber of this ventricle would have to be empty at systole in comparison to the 80 cc. systolic volume of the right ventricle.*

* d_o = thickness of wall before stretch begins (as at systole)

d_{eff} = effective wall thickness when stretched (as at diastole)

d_{act} = actual wall thickness when stretched (as at diastole)

r_o = radius at which stretch begins (as at systole)

r = radius (as at diastole)

$d_{eff} = \left(\frac{r_0}{r}\right) d_0$ Brody and Quigley[27a] $d_{act} = \left(\frac{r_0}{r^2}\right)^2 d_0$ Frank[27b]

These two formulas have the relationship,

$$\frac{d_{eff}}{d_{act}} = \frac{r}{r_0}$$

(*continued on following page*)

Relative Chamber Weights and Concepts of Failure

The correlation of the changing myocardial weights of the two ventricles with the concepts of failure is as difficult as the explanation of their relative efficiencies. Cardiac failure is the inability of the heart or a ventricle to supply the tissues with required blood. The phenomena of venous congestion, edema and increased blood volume with accompanying symptoms constitute the syndrome of congestive failure. The exact mechanism of congestive failure is controversial, there being two types of failure and two concepts for the mechanism of failure. The types of failure are low output and high output; the two concepts of congestive failure are the "backward" and the "forward." According to the "backward-failure" theory, the left ventricle fails to pump sufficient blood which then accumulates in this chamber and is dammed back into the pulmonary bed, right side of heart, and venous system.[28] The "Lungenstarre" or pulmonary rigidity due to congestion from left heart failure described by von Basch[29] in the latter part of the nineteenth century has been fully elaborated by Harrison.[30] According to the current "forward-failure" theory the diminished cardiac output leads to a proportionally greater decrease in splanchnic flow. The renal tissue is thought to be very sensitive to these circulatory changes,[31] and although normal filtration of sodium is maintained by constriction of the efferent glomerular arterioles, the tubular reabsorption of sodium is accelerated.[32] The resulting retention of sodium or salt leads to fluid retention, increased blood volume, venous congestion and edema.[33, 34] The increased venous pressure may aid the failing heart by increasing the filling pressure and diastolic volume.[35]

In all types of failure, acute or chronic, high- or low-output, there is a relative decrease in renal and splanchnic flow, a retention of sodium and water, a rise in blood volume and an increase in vasomotor tone.[36] But the degree of failure of the myocardium to meet the tissue needs does not parallel the degree of congestion,[37] and the evidences of congestion, such as increased blood volume edema, decreased circulatory rate, increased venous pressure, may vary independently of one another over wide ranges. Further investigations are necessary before the syndrome of congestive heart failure can be adequately explained.[37]

From the data presented in table 1, and figure 2, it is apparent that: (a) only the left ventricle hypertrophies in hypertensive individuals without congestive failure; (b) with the advent of congestive failure, the right ventricle hypertrophies progressively with the duration of failure, both auricles hypertrophy and the left ventricle also continues to increase in weight; (c) after failure has existed for over three years the two chambers diminish in weight; the reduction in weight may be more marked in the left ventricle.

The observation under (a) above suggests that the left ventricle acts as an isolated pump responding to an increased peripheral resistance, hence to increased work, with hypertrophy. Since there is an eccentric hypertrophy we may conclude that the right ventricle does not hypertrophy through a generalized stimulus of the scroll muscles encompassing both right and left ventricles.[38] In this study it was not possible to determine the presence of left

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At a diastolic volume of 140 cc., with an ejection of 60 cc., and a systolic residual of 80 cc., then $\frac{r}{r_0} = \frac{3.22}{2.68}$;

the general relation of $\frac{r}{r_0}$ at a constant 60 cc. ejection will be $\dfrac{\sqrt[3]{\frac{3(V_0 + 60)}{4\pi}}}{\sqrt[3]{\frac{3V_0}{4\pi}}}$

in which substitution of $V_0 = \frac{4\pi r_0^3}{3}$ yields $\sqrt[3]{\frac{r_0^3 + 14.31}{r_0}}$.

If the d_{eff}/d_{act} is increased 2.14 times over that at 140 cc. diastolic volume, then

$$\frac{r}{r_0} = \frac{3.22}{2.68}(2.14) = \sqrt[3]{\frac{r_0^3 + 14.31}{r_0}};$$

$r_0 = 0.811$; $V_0 = 2.23$ cc. This assumes that the ventricles are spherical, that the radius is for the contained volume, and that the thick-walled contractile ventricles are comparable to a thin-walled viscus.

ventricular failure unaccompanied by right ventricular failure, but the right ventricular weight increases only after the advent of congestive failure. This is to be expected if the myocardial bulk of a chamber is proportional to work performed since the pulmonary arterial and right ventricular pressures are elevated in left ventricular failure.[39]

According to the "backward-failure" theory, blood would be dammed back into the lungs from the failing left ventricle. Comparable to the response of the left ventricle to the increased peripheral resistance of hypertension, the right ventricle responds to the impaired flow of blood through the lungs into the left ventricle by increased pressure and work. "Forward-failure" might lead to an increase in blood volume, venous pressure, and filling pressure of the right heart with dilatation and, if Starling's postulate is correct, with increased work. Since the output cannot be increased above that of the weak left ventricle, pressure becomes the elevated component of work.

The apparent continued hypertrophy of the left ventricle after the onset of failure is not easily explained by either "forward" or "backward" failure theories. It is possible that the cases with cardiac failure represent a group separated from the others on the basis of a more marked hypertrophy which has "outstripped the capillary bed."[40, 41, 42]

As discussed above, one possible explanation for the greater efficiency of left as compared with right ventricle may be a smaller residual systolic volume of the former. Since an equal volume is ejected by the two chambers, those fibers encompassing the smaller volume contract over a greater distance. Through the completeness of contracture this may increase the work performed per gram of myocardium. When the ventricle fails, the accompanying dilatation stretches out each muscle fiber but also requires less contracture of each fiber to eject the original volume of blood. Increasing increments of chamber volume require progressively less contracture distance of their fibers. The most marked changes will occur in the chamber of smaller initial volume, such as has been suggested for the left ventricle. If this is true, the right ventricle with its greater initial volume would have more "reserve" in failure since the increasing systolic residual volume would affect it less. If the stretched fibers of the dilated chambers now become adjusted to their new length (thus acquiring a new "initial length") for instance through hypertrophy, the myocardium will again be able to perform more work but may be less efficient per gram of myocardium than before. The decreased efficiency of the dilated ventricle may explain the continued hypertrophy of the left ventricle after the advent of congestive failure.

This brings us to the role of dilatation in the stimulation and mechanism of hypertrophy. On one hand, dilatation is regarded as a means of increasing work performance and on the other hand, "beyond a certain optimum," it is considered as an evidence of myocardial weakness. Some consider that dilatation always precedes hypertrophy but roentgenographic studies in man indicate that hypertrophy advances without dilatation or that the two processes occur gradually and concomitantly. Whether or not a dilated, "failing" ventricle can continue to hypertrophy without undergoing compensation has not been established.

Other factors which may be operative but are difficult to assess should be mentioned: (a) intermittent periods of compensation brought about by rest, digitalis, and diuretics, (b) alterations in cardiac rhythm, (c) hypoxia during failure as a possible direct stimulus to myocardial hypertrophy or as an indirect influence through altered blood volume, and blood viscosity.

It would appear that the changes in the weights of the cardiac chambers presented in this paper cannot be entirely explained by the present concepts of cardiodynamics and cardiac failure.

Summary

1. By the use of a comparatively simple technic the weights of the different myocardial chambers have been studied in 130 cases of hypertension both with and without failure.

2. In the absence of failure only the left ventricle hypertrophies, but with the advent

of congestive failure the right ventricle hypertrophies along with a continued increase in the left ventricle. The right ventricle continues to hypertrophy with the duration of failure up to three years; after this time there is an apparent decline in the right and especially the left ventricular bulk.

3. An attempt has been made to correlate the work of the left ventricle with the weight of left ventricular myocardium in grams per square meter of body surface.

4. The left ventricle performs at least twice as much work per gram of myocardium as does the right ventricle. Several possible explanations for the apparent greater efficiency of the left ventricle are presented. The possible influences of the surface-volume or contracture-distance factor as well as the "effective wall thickness" are considered.

5. The changes in chamber weight before and after failure are discussed in relation to the concepts of congestive heart failure.

Sumario Español

El peso del miocardio de las diferentes cavidades del corazón fué determinado en 130 casos de enfermedad cardiovascular hipertensa con y sin decompensación. El ventrículo izquierdo se hipertrofia antes y prosigue hipertrofiandose después que la decompensación aparece. El ventrículo derecho y ambas aurículas se hipertrofian solamente después que la decompensación aparece. Correlacionando el trabajo ventricular con la masa muscular, el ventrículo izquierdo aparentemente produce dos veces mas trabajo por gramo de músculo que el ventrículo derecho. Varias posibles explicaciones para esta aparente mayor efficiencia del ventrículo izquierdo se presentan. Los cambios en el peso de las cavidades cardíacas se discuten en relación al concepto de la decompensación cardíaca.

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"Phlebodynia"—A New Epidemic (?) Disease

By JOHN S. PEARSON, M.D.

During the fall and winter of 1950–1951 a group of student nurses was seen with a syndrome, which, to our knowledge, has not been reported previously. The common characteristic of all cases was incapacitating pain and exquisite tenderness along the course of the superficial venous tracts of one or more extremities. Numerous clinical, epidemiologic and laboratory investigations were made without establishing a specific etiologic diagnosis. Several cases are reported in detail to illustrate the condition.

WITH the coinage of a new name and, by inference in the title, the claim of a new disease, the author freely admits that both name and claim arise from our inability to pigeonhole a recent experience into the previously known categories of disease states. The name was chosen because the characteristic symptom in the group of cases seen was severe pain and exquisite tenderness over the course of the superficial veins of the lower extremities. The word "epidemic" was used as an adjective because the 22 cases seen occurred in a relatively close group and in a relatively short period of time.

During the fall and winter of 1950–1951 we saw 19 student and three graduate nurses between 17 and 26 years of age in St. Mary's Hospital, Huntington, West Virginia, who presented themselves for medical attention because of incapacitating pain in one or both lower extremities. Physical examination was negative except for the site of the presenting complaint. Without exception there was exquisite tenderness somewhere along the course of the superficial veins of one or both legs, associated with the presence on palpation of a cord-like structure along the course of maximum tenderness. Frequently there was a positive Homan's sign, and slight swelling of the affected leg. Occasionally there were other concomitant or intercurrent complaints such as headache, gastrointestinal upsets and lower abdominal pain. Minimal temperature elevations occurred in some cases, but this was not universal. There was no generalized muscle tenderness, no involvement of the peripheral arteries, no evidence of arterial occlusive disease or Reynaud's phenomenon, and there was no evidence of lymphedema or lymphangitis. Although 19 of the 22 cases were student nurses in one nurses home, and in spite of the fact that the accumulation of cases after the first one suggested a communicable disease epidemic, epidemiologic studies by representatives of the National Institute of Health were completely negative. Laboratory studies performed were all negative. These included routine blood counts, urinalyses, erythrocyte sedimentation rates, heterophile antibody tests, studies of blood smears, serology, aerobic and anaerobic blood cultures, and antistreptolysin titer studies. Microscopic studies of biopsied material failed to show the typical findings of any known disease. Bacteriologic, fungus, virus and rickettsial studies on the biopsied material were likewise negative. No parasites, such as trichina, were seen on careful search. Consultation with leading vascular specialists in different clinics failed to help establish a diagnosis. Neurologic consultations were also unrevealing. Empiric trials at therapy with all antibiotics, anticoagulants, and corticotropin (ACTH) were without effect upon the course of the process, which fortunately was self-limited. The following illustrative case reports typify the course seen.

From the Medical Service, St. Mary's Hospital, Huntington, West Virginia.

CASE REPORTS

M. C., a 19 year old student nurse, first sought medical attention on Oct. 17, 1950, with the history of pain in the left leg for two days. The pain had become so severe that she was no longer able to walk or continue her duties on the hospital floors. On examination she was found to have a slightly swollen left leg with marked tenderness to gentle palpation over the saphenofemoral junction. At this point there was a cord-like structure about 6 cm. in length. Extreme tenderness was elicited by pressure or squeezing of the left calf. There was a positive Homan's sign. A tentative diagnosis of spontaneous

thrombosis of the superficial femoral and saphenous veins was made. Her blood pressure was 115/90, the temperature was 99.0 F., the pulse rate was 88, and respirations 20 per minute. Routine laboratory studies revealed a red blood count of 4.53 million, with a 90 per cent value for the hemoglobin. The white blood count was 7,900 with 53 per cent neutrophils, 46 per cent lymphocytes, and 1 per cent eosinophils. The urine was normal except for a trace of albumin with 15 to 20 white blood cells per high-power field. She was treated conservatively with a vasodilator (Priscoline) drug, penicillin, and dicumarol. The prothrombin concentration level was maintained between 12 and 23 per cent. Pain was continuous for about six days, and there was a daily spiking of the oral temperature to about 100 F. for 12 days. November 4, the seventeenth hospital day, she was discharged from the hospital to the nurses home to remain off work for approximately another week.

Second admission. November 22 she presented herself again with the same complaint, a recurrence of pain in the left leg. Again a tentative diagnosis of thrombophlebitis was entertained and a surgical consultation was requested. The surgeon advised ligation and this was done on the day of admission. The surgeon commented that although there was considerable perivascular reaction, division of the supposedly affected vein revealed no thrombus. Penicillin and dicumarol were again given and the patient was allowed out of bed on the third postoperative day without pain and was discharged on the sixth postoperative day.

Third admission. December 21 she was again admitted, this time with the history of pain in the right leg, in every way similar to her previous experience with the left. She had first noticed the pain four or five days previously, but had not given in to hospitalization until the pain had become so intense that she could no longer stand or walk. A positive Homan's sign was now present on the right, and there was definite induration in, and exquisite tenderness over, Hunter's canal, in the right popliteal space and over the right calf. The temperature was 99.2 F.; the white blood cell count was 7,950 with 56 per cent neutrophils, 42 per cent lymphocytes and 2 per cent basophils. The urine was normal in all respects. An x-ray film of the chest showed only calcified hilar nodes on the right with several small calcified lesions distributed throughout the right mid-lung zone. Dicumarol was started. December 24 she began her regular menstrual flow, but this time "flooded" as compared with her previous menses. Dicumarol was discontinued and vitamin K therapy was begun. Chloromycetin, 2 Gm. daily in four doses, was started empirically and continued for 10 days without evident effect. December 28 and 29 the temperature spiked to 101.6 and 101.8 F. Blood cultures and febrile agglutinations were negative. A repeat complete physical examination was again negative except for the quite tender leg. January 7 she began to complain of severe headaches which were unaffected by aspirin in doses of 0.6 Gm. January 9 she was asymptomatic and was discharged January 13. She had occasional recurrences of pain lasting for a day or so at a time in one or the other leg for another two-month period before she was finally considered to be well.

M. A. E., an 18 year old student nurse, first sought medical care on Nov. 16, 1950 with what appeared to be a superficial phlebothrombosis of the right leg. She was treated conservatively with anticoagulants and discharged after a period of ambulation December 12. She returned to her work on the floors of the hospital, but was only able to continue this routine for two days when she developed a recurrence of the pain in both legs, extending upward from the calf through the popliteal space and along the course of the saphenous vein into the groin. By this time some 10 or 12 nurses were in the hospital as patients with a similar picture. In an attempt to further study the unknown disease process, we subjected two of the girls to vein exploration and biopsy. This patient (M. A. E.) was one of the two so studied. The surgery was performed on Jan. 7, 1951. The surgeon described considerable periphlebitis, but as in our one experience in the case previously outlined, there was no thrombus in the lumen of the vein. January 15 she developed an acute coryza and the pain in the legs was reported as being much worse during this infection. On January 22 a paraspinal block was performed on the right at D-12, L-1, and L-2. The leg pain was ameliorated, but not abolished, for a period of about 16 to 18 hours by this procedure. January 24 spinal anesthesia was administered, but this gave relief from the pain for only about three hours. As a result of the long hospitalization and the doubtful diagnosis, a considerable psychosomatic element was thought to be present in this case during the latter days of the disease. She was discharged from the hospital January 29, but for another three months she was seen to limp occasionally about the wards and she said she was having some pain in her legs at those times.

J. Y., a 20 year old student nurse, was first studied on Nov. 15, 1950, giving the history of sudden onset of pain in the left popliteal space approximately 24 hours previously. This pain had been practically continuous and had been followed shortly by a feeling of "numbness" down the back of the leg to the toes. On examination, the only abnormalities were found in the left lower extremity. The calf was markedly tender, there was an exquisitely tender spot in the popliteal space, Homan's sign was positive, but arterial pulsations were good and equal bilaterally. By November 21 she complained of pain extending up into the groin; examination revealed a tender cord-like structure along the inner aspect of the left thigh in Hunter's canal. The pain gradually subsided, but December 5

she experienced the sudden onset of pain in the lateral base of the right chest. Physical examination revealed no abnormalities and the serially repeated chest x-ray films were negative. She was discharged asymptomatic on December 11.

Second admission was on Dec. 20, 1950, with recurrence of pain in the same leg, identically as in the first admission. An empiric trial of Chloromycetin was made without evident benefit. On Jan. 7, 1951, she was subjected to vein biopsy of the left saphenous vein. The surgeon's operative note on this case was that the vein appeared grossly normal and there was no thrombus within its lumen. The pathologist's report was "intimal sclerosis of undetermined origin." February 3 corticotropin (ACTH) in 12.5 mg. doses was given every six hours for six doses without effect. Symptoms gradually diminished and she was discharged after being incapacitated for almost three months

Discussion

The first two cases to develop the illness we are discussing were thought to represent cases of recurrent phlebothrombosis, although they did not present the usual phenomena of arterial spasm, skin discoloration, or edema of the involved extremity. One of these first cases was subjected to ligation and resection. On resection, the vein wall was thought to be thickened, but no thrombus was found. After more and more cases of what appeared to be the same process occurred in the student nurse population, we felt that there might be an epidemiologic problem. With this in mind, the Communicable Disease Laboratory of the National Institute of Health was called in. The representatives of this organization spent several days exhaustively studying all aspects of the outbreak without any positive results. Blood and serum specimens were collected from all cases and subjected to innumerable tests, cultures, and agglutinations without positive results. More veins were sectioned and sent to various pathologists, but there was no uniformity of opinion among them, nor was there a specific diagnosis suggested. Dr. M. B. Dockerty of the Mayo Clinic reported as follows:

"Subacute phlebitis, limited strictly to the vasa vasorum. The majority of the involved vessels are filled with leukocytic thrombi, many of which contain eosinophils as well as polymorphonuclear leukocytes. In a few of the vessels these inflammatory cells invade the walls of the vasa vasorum and in a few, perivascular cuffing is noted. Endothelial swelling and edema are noted in vessels not containing the thrombi. The endothelium and wall of the large vein removed are practically normal except for a mild degree of fibrosis."

Our pathologist thought there was some definite evidence of intimal swelling. All surgeons noted the increased fibrosis surrounding the affected veins, but in none of the cases submitted to surgery was there a thrombus within the vein. On the suggestion of the staff of the hospital, many of the newer antibiotics plus penicillin and streptomycin were given an empiric trial without effect. On the suggestion of Dr. Olsen of the National Institute of Health, we tried corticotropin (ACTH) in small doses, which was also without effect. (We are indebted to the Communicable Disease Laboratory of the National Institute of Health for the supply of ACTH used.)

Bed rest with elevation of the leg over a long period of time has caused at least a remission. There was a recurrence in several cases, the recurrence in three cases occurring after about a month's freedom from pain. One of these latter cases was sent to one of the foremost vascular clinics in the Middle West for study, but we still do not have a specific or etiologic diagnosis.

Summary

A previously unreported syndrome occurring in a group of 22 student and graduate nurses is reported. This syndrome has as its outstanding feature incapacitating pain and tenderness along the course of the superficial veins of the lower extremities. Mortality was nil, but morbidity was long. No specific therapy has been found.

Sumario Español

Durante el otoño e invierno de 1950–51 un grupo de enfermeras presentó un síndrome que de acuerdo a nuestros conocimientos nunca ha sido reportado previamente. La característica común al grupo fué un dolor incapacitante y sensibilidad marcada en el curso de venas superficiales de una o más extremidades. Numerosos estudios clínicos, epidemiológicos y de laboratorio fueron hechos sin poderse establecer una causa etiológica.

Cardiovascular Lesions in Arachnodactyly

By Edwin M. Goyette, Col., MC, U.S.A., and Paul W. Palmer, Capt., MC, U.S.A.

The cardiovascular lesions in 34 cases of Marfan's syndrome which were studied post mortem are reviewed. Recent reports show that the most common and most important lesion is cystic necrosis of the media which results in aneurysmal formations of the ascending aorta. The aneurysm may be fusiform and the aortic ring dilated, producing a marked aortic insufficiency, or there may be a dissecting aneurysm, either recent or chronic. Valvular lesions are common but probably not important. Septal defects are occasionally encountered but are not functionally significant.

ARACHNODACTYLY (Marfan's syndrome) is a relatively rare disorder characterized by widespread disturbances in the development of tissues of mesoblastic origin. Disability may be caused by the skeletal and ocular deformities which result, but death, which is usually premature, is due to involvement of the cardiovascular system. The disease is well known to ophthalmologists and pediatricians and is frequently described in the ophthalmologic and pediatric literature. We wish to report another case and to briefly summarize the usual features and to emphasize the cardiovascular lesions associated with it, particularly those involving the aorta and the valvular endocardium.

Case Report

A 23 year old corporal was admitted to Fitzsimons Army Hospital on Oct. 28, 1951, complaining of intense dyspnea and orthopnea. The patient's family history was negative. He had always been extremely tall and slender and had a pigeon chest deformity. He had been in good health until the age of 16 when he noted that he tired more easily and became somewhat short of breath on strenuous exertion. In 1946 he was told that he had a heart murmur. He was inducted into the Army on Nov. 15, 1950 and his cardiovascular system was considered normal. Three weeks later he was admitted to a hospital complaining of shortness of breath which had come on suddenly. There was no chest pain. Physical examination at that time showed no abnormality of the cardiovascular system. He was discharged five days later. He got along well until Sept. 16, 1951. On that date, while playing cards, he suddenly complained of pain in his chest and back, dyspnea, and began to perspire profusely. He was hospitalized and for the first time, abnormalities of the cardiovascular system were noted. The cardiac impulse was diffuse and there were loud systolic and diastolic murmurs at the base of the heart. His blood pressure was 130/80, respirations 22, and pulse rate 80. There was no evidence of congestive heart failure. A few days later it was noted that he had marked pulsations of the carotid arteries; the peripheral pulsations were of the Corrigan type; and the apical impulse was visible and palpable in the sixth intercostal space at the anterior axillary line. The aortic second sound was loud and tambour-like. There was a grade III, early, blowing, diminuendo, diastolic murmur, maximal in the third left intercostal space. There was a short, soft, grade I systolic murmur at the aortic area. A diastolic gallop rhythm was present. His blood pressure was 144/42.

Laboratory studies revealed a slightly elevated white cell count and an elevated sedimentation rate. Electrocardiogram revealed a sinus tachycardia with a right bundle branch block. Chest x-ray films showed pulmonary congestion and slight generalized cardiac enlargement. While in the hospital the patient continued to have a tachycardia, his dyspnea progressed, and he developed orthopnea, signs of pulmonary congestion and an enlarged, tender liver. It was thought that he had rheumatic heart disease with aortic insufficiency and, because of a persistently elevated sedimentation rate and slight fever, that he had active rheumatic carditis. He was transferred to Fitzsimons Army Hospital.

Physical examination on admission showed a very tall, slender, white man, who was 76 inches tall and weighed 151 pounds. The fingers were long and narrow. The lower jaw was prominent. The ears were long and pointed. The forehead was high and the patient had an old, sad appearance. Eyegrounds were normal. The palate was high and arched. There was a pigeon breast deformity. The cardiac findings were essentially as previously described.

The initial impression was rheumatic heart disease, active, with aortic insufficiency and mitral stenosis, with left ventricular hypertrophy and left auricular enlargement. Chest x-ray films on admission are shown in figures 1 and 2. It was thought that the patient was in congestive heart failure and he was treated accordingly. He failed to respond and died rather suddenly on his tenth hospital day.

Autopsy Findings. Except for congestive splenomegaly and hepatomegaly the significant findings

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were limited to the cardiovascular system. The heart weighed 698 Gm and appeared dilated in all chambers. The left ventricular wall averaged 2.1 cm. in thickness and the right ventricular wall 0.5

FIG. 1. Postero-anterior chest x-ray film.

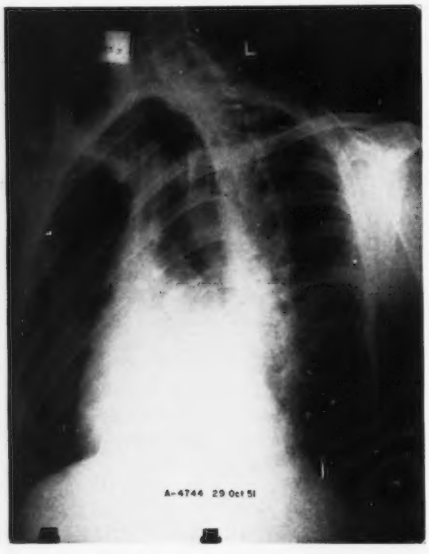

FIG. 2. Left anterior oblique view.

cm. The valve cusps were thin and delicate. The aortic valve was incompetent and measured 12 cm. in circumference. The foramen ovale was patent measuring 1.6 cm. in diameter. The coronary arteries were normal except the right artery arose 5.0 cm. above the coronary ring. The aorta above the aortic valve showed an aneurysmal dilatation with a circumference of 13 cm. There was a sharp break in the intima of the aorta 6.5 cm. above the aortic ring, and at this point the aorta became a tube within a tube (fig. 3). At the beginning of this dissecting aneurysm the outer tube was 9.6 cm. in circumference while the inner was 6.0 cm. The inner tube was incompletely separated from the outer. The dissecting aneurysm extended through the entire length of the aorta and into the innominate artery for a distance of 3.0 cm., into the left common carotid for 0.3 cm., into the left subclavian for 5.0 cm., and into each common iliac artery for 3.5 cm. The end of the dissection in these vessels was clearly defined and sharp. The lumina of all branches of the aorta communicated with the lumina of both tubes of the dissecting aneurysm except the left renal artery which had no communication with the outer

FIG. 3. Aorta.

tube. The outer tube was corrugated and "geographic" in appearance but was lined by a smooth membrane, only slightly rougher than the normal intima.

Microscopic examination of the heart showed hypertrophy of the myocardial fibers. The sections of the aorta showed the dissection occurring between the outer and middle thirds of the media. Sections taken from the aneurysmal portion of the aorta proximal to the dissecting aneurysm showed cystic spaces in the media filled with lightly basophilic fibrillary and finely granular material. There was a numerical reduction and disorganization of smooth muscle cells. Elastic tissue stains showed marked disruption, fragmentation, and condensation of elastic fibers with indistinct internal and external laminae (fig. 4). The final diagnoses were: (1) Marfan's syndrome. (2) Dissecting aneurysm of the aorta.

DISCUSSION

Arachnodactyly was first described in 1896 by Marfan,[1] who called it dolichostenomelie.

Achard[2] in 1902 called it arachnodactyly (spider fingers). Salle[3] in 1912 reported the first case associated with heart disease, confirmed by autopsy. The first report in the American literature was by Piper and Irvine-Jones[4] in 1926. This report stressed the frequency with which arachnodactyly was associated with congenital malformations of the heart. About 350 cases have been described but in spite of this rather extensive literature, there have been only 33

FIG. 4. Aorta. Verhoeff's elastic tissue stain ×140.

previously reported cases with necropsy findings. Twenty-three of these have been published in the last 10 years and it is only during this period that the reports have been detailed concerning the cardiovascular system.

Detailed descriptions of the various clinical features have been given by numerous authors and are well known, so only a summary of these will be given here. The disease is frequently familial and congenital. Several cases in one family are not uncommon.[5] The affected person is slender and often abnormally tall. The limbs are disproportionately long and the more distal segments of the limbs show a relatively greater increase in length. The fingers are long and thin, having been described as spider-like and are the outstanding characteristic of the disease. The head is usually dolichocephalic. The face is long and thin and appears prematurely old. The ears are long and pointed and the lower jaw juts forward. The teeth are usually long and narrow. The palate is high and arched. These features, coupled with the wearing of glasses, which is seen in the majority of patients, tend to give them a serious, prematurely aged, wise appearance. Their apparent slenderness is aggravated by a scanty amount of subcutaneous fat and a poorly developed, hypotonic musculature. The ligaments are lax and poorly developed, permitting increased mobility of the joints which may be marked enough to allow dislocations. There are frequent spinal and thoracic deformities which are often thought to be the result of the inadequate muscular development. However, these deformities have been noted before the child is able to sit or walk. The most common spinal deformities are kyphosis and scoliosis but funnel chests and pigeon breasts are frequently seen.

Ocular abnormalities are present in about 50 to 75 per cent and are often characteristic. These include congenital bilateral dislocation of the lenses and because the lens is unsupported, the iris often appears tremulous (iridodonesis). Myopia is the rule. The pupils are usually small and respond poorly to mydriatics. The vision is seriously impaired and may progressively deteriorate.

The incidence of lesions of the cardiovascular system is uncertain but has been reported as being present in 30 to 60 per cent. The exact incidence is difficult to determine because many of the patients are seen by ophthalmologists only and have been recorded only for their ophthalmic interest and external appearance. Another difficulty is that cardiac lesions may not become apparent until shortly before death. Murmurs are frequently described, but in view of the severe spinal and thoracic deformities

often present, such findings may not be indicative of organic heart disease unless supported by other evidence.

All of the above deformities may be present in a single case of arachnodactyly and there is no difficulty in recognizing a typical case in which the triad of skeletal, ocular and cardiac abnormalities are all present. As a rule, one or more features will be missing and the presence of the commonest characteristic is sufficient for the diagnosis. The less complete cases may go undiagnosed unless the condition is borne in mind. In some cases the diagnosis may be impossible unless the disease is also present in relatives in a more typical form.

TABLE 1.—*Cardiovascular Lesions in 34 Patients with Arachnodactyly*

Aortic Lesions		22
Dissecting Aneurysms[14, 16, 17, 19, 21, 22, 24, 28, 29]		12
Fusiform Aneurysms[13, 18, 25-27, 29]		7
Dilated Aortic Ring[5, 7]		3
Endocardial Lesions		21
Valvular		21
Mitral[5, 7, 9, 10, 12, 13, 17-21, 25, 28, 29]	15	
Aortic[3, 5, 7, 9, 13, 17, 25, 28, 29]	10	
Tricuspid[3, 17]	2	
Not specified[24, 28]	2	
Mural[13, 17]		2
Combined Aortic and Endocardial Lesions		13
Septal Defects		9
Patent Foramen Ovale[3, 6, 13, 23, 29]		7
Inter-auricular[4]		1
Patent Ductus Arteriosus[8]		1
Dilated Heart (no other data given)[11]		1
Normal Heart[15]		1

The syndrome affects both sexes equally, probably occurs in all races but most frequently in the white. The etiology is unknown but thought to be a congenital defect.

Cardiovascular Lesions

The cardiovascular lesions of the 34 patients whose postmortem findings are known are summarized in table 1. The initial reports[3, 4, 6] indicated that congenital septal defects were the most common anomalies to be found. More recent studies show that this is not true as there have been only eight such defects found. These were all of questionable clinical significance and four were associated with aneurysms of the aorta and one with valvular lesions.

The most common lesion encountered has been involvement of the aorta which was found in 22 patients. In addition, there are reports[18, 26, 28] of patients with aortic insufficiency or with definite evidence of aortic aneurysm on fluoroscopy but without post-mortem confirmation. Several other cases of sudden death without autopsy examination have been reported in young patients with arachnodactyly.[25]

The gross descriptions have differed in detail. A few patients have shown only a dilated ring, others have shown a fusiform or saccular aneurysm and others have had a dissecting aneurysm. The aneurysms usually begin just distal to the aortic valve, are usually fusiform in shape and may be very large. They usually are rather short, ending just beyond the innominate artery but they may extend as far as the left subclavian or into the abdominal portion of the aorta. They frequently end abruptly and not uncommonly are associated with narrowing or stenosis of the aorta and two have been associated with coarctation.[19, 26] Some of the dissecting aneurysms have ruptured, producing death, while other dissections have been chronic and become healed. Another common finding has been a high origin of the coronary arteries, particularly the right.

Although the gross appearance varies widely, the microscopic description is usually identical. In both the fusiform and dissecting types the essential lesion is always in the media, the elastic and muscle fibers are deficient and replaced by loose, collagenous, fibrous tissue. It is generally felt that the lesion is indistinguishable from "medionecrosis aortae idiopathica cystica" as first described by Erdheim[30] as the cause of dissecting aneurysm in middle aged and elderly people with hypertension.

The most consistent clinical features of aortic involvement are the complaint of chest pain and the signs of aortic insufficiency. The chest pain is usually substernal in location but not infrequently is also present in the back. The pain is very similar to angina pectoris except that it is frequently of longer duration. Only one patient had the complaints typical of dissecting aneurysm. She was suddenly seized

with severe, oppressive, tearing pain. The next most common complaint is that of dyspnea on exertion. Sometimes this has been present without any signs of cardiac failure. It is usually the initial symptom in those patients who die of congestive heart failure. Signs of marked aortic insufficiency are frequently described prior to death.

A common description is that of a young person with arachnodactyly whose heart is usually considered normal until the patient reaches the early teens. Then a routine examination often reveals a systolic murmur which is usually along the left sternal border or at the apex and the heart may appear slightly enlarged. Both findings are apt to be explained on the basis of the chest deformity which is usually present A few years later the classical signs of aortic insufficiency are found.

Chest x-ray films and fluoroscopic examination with barium have been very disappointing and often misleading because a definite aneurysm is not usually demonstrated. The most common finding on chest x-ray study is generalized cardiac enlargement, particularly involving the left ventricle. The pulmonary artery is often described as being prominent and definite enlargement of the left auricle is frequently demonstrated.

Only a few reports mention the electrocardiographic findings. A bundle branch block was described in four patients,[18, 24, 27] in three of whom it involved the left bundle branch system. The pattern of left ventricular hypertrophy or left heart strain was reported five times[25, 29] and partial auriculoventricular block has been described in three patients.[13, 24, 27] Auricular fibrillation was noted three times.[13, 21, 24]

The most common cause of death is congestive heart failure, usually the result of the marked aortic insufficiency. Sudden death is common and is usually due to a dissecting aneurysm.

The next most common lesion is involvement of the valvular and mural endocardium, noted in 21 patients, and which is frequently considered as evidence of rheumatic heart disease. Some authors[31] described typical cases of arachnodactyly which had recurrent illnesses that seemed to be rheumatic fever. The usual finding in the valve is that the leaflets are rolled and thickened, frequently described as bolster or cushion shaped, the cusps may be thickened and shortened, the edges are often hard and nodular, and fenestrations of the cusps have been described. Occasionally the chordae tendineae are shortened. Aortic insufficiency, if present, was always due to the aneurysm, not to aortic endocarditis. Several patients were thought to have mitral stenosis on clinical grounds but autopsy showed normal mitral valves or minimal involvement without stenosis but with a marked dilatation of the aortic ring which produced an Austin Flint murmur at the apex. Microscopic examination of the involved valves rarely ever confirmed the presence of rheumatic fever. The usual finding is that of collagenous thickening or a myxomatous fibrosis similar to that seen in normal infants and on valves of hearts with congenital heart lesions. Examination of the myocardium also fails to reveal the evidence of previous rheumatic infection. The similarity to rheumatic fever is frequently increased by the x-ray findings because of an enlarged left auricle and a prominent pulmonary artery. Also, it is not unusual for these cases to run a low grade fever which was present in one third of the reported patients. The diagnosis is further complicated by the frequent presence of well marked aortic insufficiency without the demonstrable evidence of aortic aneurysm. The electrocardiogram has tended to add to the confusion because both patients who showed partial auriculoventricular block and all three patients who showed auricular fibrillation had aneurysms of the aorta. Generally speaking, the valvular lesions have not been important factors in the autopsied cases.

In view of the frequency of aortic aneurysm in arachnodactyly, it is interesting to speculate on how many cases of aortic aneurysm in normotensive adolescents and young adults may have skeletal changes without the significance of these being recognized. The lesion of the aortic wall seems to be identical with that found in most aneurysms, other than syphilitic, and the etiology may be the same. Although aneurysms have been considered rare in young

persons, Schnitker and Bayer[32] found 141 of 580 dissecting aneurysms to be in persons under the age of 40. These authors concluded that medionecrosis was the usual cause and this conclusion has been confirmed by others. Cystic medionecrosis is the basis of nearly all dissecting aneurysms regardless of age.

Fusiform aneurysms are much rarer at this age; Bronson and Sutherland[33] collected descriptions of 12, the eldest patient being 26 years. Fusiform aneurysms have been described[34] in young adults in which histologic examination has shown cystic medionecrosis. There have been occasional patients with dissection of the aorta with a fusiform aneurysm.[35] Thus, the pathologic process in the aortic wall seems to be identical whether the aneurysm is dissecting or fusiform. It seems almost incredible that an identical pathologic process can be found in different types of aortic aneurysms unless there is some causal relationship. On the other hand, the good development and athletic ability in young people dying suddenly of a ruptured aneurysm is often stressed. This fact would tend to exclude arachnodactyly except in a "forme fruste."

It is conceivable that cardiac lesions, particularly dissecting aneurysms or aortic dilatation, can occur as an isolated lesion in some families with arachnodactyly. Other components of the triad have been reported as isolated lesions.[5] It is of interest that the family history is most often positive when the disease is mild. A recent report[36] described two patients with chronic dissecting aneurysm which simulated rheumatic heart disease. One case had arachnodactyly in addition to the typical findings in the aorta so this doubtless represents another case of Marfan's syndrome which was missed clinically. A diagnosis of dissecting aneurysm or aortic dilatation in a young person should therefore lead to a search for arachnodactyly in the patient and amongst his family. The possibility of aortic aneurysm should also be remembered in known cases of arachnodactlyly or where there is a positive family history.

Summary

Another case of Marfan's syndrome that died of cardiovascular disease is reported. The cardiovascular lesions in arachnodactyly have been reviewed and discussed. They are common and are an important cause of death. They include aortic medial necrosis and endocardial lesions. The former is more dangerous as it leads to dilatation of the aortic ring producing aortic insufficiency which results in marked left ventricular hypertrophy and dilatation with death from congestive heart failure, or the disease of the aortic wall may result in aneurysmal formation which may rupture or dissect. A fusiform or dissecting aneurysm in normotensive adolescents or young adults may represent a "forme fruste" of arachnodactyly.

Sumario Español

Las lesiones cardiovasculares en 34 casos del síndrome de Marfan que fueron estudiados con autopsia se revisan. Reportes recientes demuestran que la lesión más común y más importante es necrosis cística de la lámina media que resulta en formaciones aneurismicas de la aorta ascendente. La aneurisma puede ser fusiforme y el anillo aórtico puede estar dilatado produciendo una insuficiencia aórtica, o un aneurismo disectante, reciente o crónico. Lesiones valvulares son comunes pero probablemente no importantes. Defectos del tabique son ocasionalmente encontrados pero funcionalmente sin importancia.

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Mercurial Diuretics: The Replacement of Parenteral Administration by a New Oral Preparation in Ambulatory Patients with Chronic Congestive Heart Failure

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Improvement in the usage of an effective therapeutic agent is highly desirable especially when the method of administration is simplified, the total dosage reduced, the toxicity of the drug diminished and the cost of medical care lessened. The replacement of parenteral injections of the mercurial diuretics by an oral preparation in ambulatory patients in chronic congestive heart failure represents a step forward in the management of this type of patient.

THE INDUCTION of diuresis in chronic congestive heart failure by injection of mercurial preparations is the most rapid, effective and reliable method available today.[1, 2] Very often the control of the symptoms can be sustained only by so-called "maintenance doses" of the diuretic at frequent intervals.[2, 3] The chief hazards of this form of therapy arise because of hyponatremia[4, 5, 6] and digitalis intoxication[7, 8, 9] due to the mobilization and loss of fluid from body tissues. Because the widespread use of self-administered parenteral diuretics remains to be established[10] many patients must seek the services of a doctor or nurse at frequent intervals.

In an attempt to overcome these objections, and yet retain the efficiency of the mercurial diuretics, oral preparations have been introduced.[7, 11] However, even this method has its drawbacks. To be effective, large doses of the drug must be ingested, the amounts used commonly causing nausea, vomiting, diarrhea, melena or stomatitis.[1, 11, 16] The occurrence of uremia and other types of renal intoxication has been reported.[9] Unpredictability of action still remains a problem.[1] Because of these very real obstacles the search for a less objectionable oral mercurial diuretic continues.

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METHODS AND MATERIALS

The purpose of this study was to attempt replacement of parenteral mercurial diuretics by a new oral drug labeled Ex 1431.* Thirty-five patients who had been in congestive failure ranging in duration from 1 month to 11 years were observed at the Adult Heart Clinic of the Los Angeles County Hospital. There was no selection of patients. All were ambulatory, and most of them had been receiving maintenance doses of digitalis preparations, and had also been placed on low-sodium diets.

The dosage of the tablets varied; most often it was one tablet three times per day, twice weekly three or four days apart. Some patients received one tablet three times per day, once weekly, others three times weekly. On occasion one tablet twice daily, five days a week was given.

The period of observation varied from 1 to 11 months. At first patients were observed weekly for signs and symptoms of gastrointestinal or renal toxicity or other signs of intolerance, later they were seen at intervals of one month or more.

It is to be emphasized that prior to substitution by tablets, most of the patients had been receiving Mercuhydrin injections once or twice per week in order to control the congestive failure. The severity of failure was therefore of moderate to marked degree. Most patients were classified grade III C, or D, as to heart function and therapy according to American Heart Association standards.

The patients studied had advanced heart disease and significant limitation of physical activity. They were comfortable at rest. Their ordinary physical

* The tablets were supplied by the Lakeside Company. The chemical composition consisted of 3-(alpha-carboxyethyl-alpha-thio)-mercuri-2-methoxypropylurea. This represented 10 mg. of organic mercury in each enteric coated tablet.

activity had been limited due to unusual fatigue, dyspnea, angina or palpitation. They had been advised to discontinue their more strenuous everyday activities and habits.

The etiologic types of heart disease listed in table indicate the presence of the four most common types. Age groups include patients from the third decade through the ninth. There were 19 males and 16 females.

Criteria for Determination of Results

Table 1† shows details of the study and summary of results. The response to the oral drug was considered as having satisfactorily replaced the response to parenteral mercurial injections if there was clinical evidence of maintenance of "dry weight" and prevention of progression of the symptoms of congestive failure. In addition, the result was good if at the end of the period of observation functional classification was the same or better than at the time of substitution of therapy. In those patients who responded well, edema and rales were minimal or absent. Some of the patients had hepatomegaly due to chronicity of their failure. If this decreased in size or remained stationary along with the other criteria, the result was considered satisfactory.

The drug was a failure if congestive symptoms progressed, or reoccurred after having been in abeyance under previous injection therapy. If the patient showed signs of intolerance or toxicity the result was also classified as unsuccessful. Control of congestive failure by oral therapy for at least one month was required before the result was considered good. Many of our patients had been getting intramuscular Mercuhydrin four or eight times a month. If this number of injections could safely be avoided, we believed this to be worthwhile.

Results

On the basis of the above criteria, 28 of the 35 patients showed good response to the mercury tablets. (See table 1.) This is equivalent to 80 per cent of this series.

Analyzing the results further, it was noted that of 14 patients with rheumatic heart disease, 11 responded satisfactorily. Other etiologic groups represented in the successful category included three of four patients with arteriosclerotic heart disease, two with cor pulmonale, two with syphilis and hypertension, seven with hypertension. Of six patients with both hypertension and arteriosclerosis three showed good results.

From the standpoint of age, 19 of the 35 patients were in the age group 50 to 70 years; 17 showed good diuresis. Two patients aged 20 to 29, and one aged 80 also showed good response.

In studying patients on the basis of duration of congestive symptoms, 11 patients responded well whose failure was from 5 to 15 years in duration, four patients in failure less than one year, and seven who had been failing from one to two years responded. Hence the effectiveness of the drug manifested itself in recent as well as longstanding failure.

Intolerance to the tablets was noted in six instances. The chief discomfort was gastrointestinal, consisting of cramping in the abdomen, nausea, occasional vomiting and diarrhea. A sour and burning sensation was noted in the mouth by one patient. It is interesting that another patient (case 9, table 1) noted that while parenteral mercurials had previously caused abdominal cramps, the oral form for a period of nine months did not do so, and that in general she felt "the best she ever has" since taking mercurial therapy. There was no evidence of renal injury.

Case Reports

Case 12. This patient had been getting mercurials for seven years. She developed congestive failure 11 years ago because of hypertensive heart disease. The number of injections summarized are: In 1944, 19; in 1945, 47; in 1946, 86; in 1947, 101; in 1948, 96; in 1949, 64; in 1950, 62; and in 1951, first seven weeks, 16.

She was placed on the tablets with a dosage equivalent to 10 mg. of mercury three times a day, twice a week; and for the 11 succeeding months was able to maintain "dry weight" as well as keep all symptoms of congestion in abeyance. There was no evidence of toxicity. She volunteered the information that she had "felt the best in a long, long time." This case points out the ease of control in some patients with 60 mg. of mercury per week. On the basis of having received about eight injections a month prior to the initiation of oral treatment, it is estimated the oral mercurials during 1951 replaced about 96 injections. Even should this have proved one-half the estimated amount, the results with tablet therapy would be considered gratifying.

Case 13. This patient had shown a gradually progressive failure in the preceding 13 years. Mercury injections had been given intermittently for the

† At the request of the Editor, table 1 is being omitted from the published paper. This table will be furnished upon request.

last five years. The congestive symptoms were especially severe in the four months prior to oral therapy. Weekly Mercuhydrin was necessary. She was given one tablet three times a day, twice weekly; later this dosage was increased to three times weekly. She was observed on this regimen for the succeeding 11 months, with evidence of good control, and absence of toxicity.

This case and case 9 illustrate the value of this new oral mercurial in instances of congestive failure of more than 10 years duration in middle-aged and elderly persons.

Case 10. This patient illustrates response to the drug in a patient with rheumatic valvular disease who had been in failure two years. In 1950 the patient had received 60 Mercuhydrin injections. In the first two months of 1951, just prior to tablet therapy, he was given 15 injections. For the following 10½ months he was given the tablets in dosage of 10 mg. three times a day, twice weekly. His weight decreased from 134 pounds to 129. Six months later his weight increased to 132 pounds; the liver was palpable three fingerbreadths below the costal margin. The dosage was then increased to 10 mg. three times a day, three times per week with improvement. This was maintained in the succeeding four months. Then his weight increased to 138 pounds and hepatomegaly recurred. He was given Mercuhydrin intramuscularly with return to previous weight. There was no toxicity while on oral therapy. Control of congestive symptoms for 10½ months in this instance indicated a satisfactory response. The probable replacement of 50 Mercuhydrin injections during 1951 is good therapeutics.

Case 24. A 60 year old hypertensive woman had been in failure three years. She had received Mercuhydrin twice weekly in the previous year. Three weeks after she was placed on oral therapy of 10 mg. three times a day, three times a week, sudden abdominal distention appeared. She was returned to Mercuhydrin twice weekly for two months with good results. She was then again started on the tablets, 20 mg. three times a day, three times per week. She did well for the following six months. Then she began to cough up bloody sputum and became increasingly dyspneic. Because of the suddenness of this occurrence she was given Mercuhydrin injections and symptoms were relieved. She did not show toxicity during the course of oral therapy.

This case illustrates the sudden storms in the course of congestive failure which can be better managed with the use of the injectable mercurial than by the oral form. However, the interim therapy with oral mercury was satisfactory.

Case 4. This patient had been in failure for one year, during which time he had been getting weekly Mercuhydrin injections. He was given 10 mg. in oral tablets three times a day, once weekly. After three and one half months his initial weight had been reduced from 172 pounds to 169, and there was no progression of failure. He then noted mild nausea and diarrhea. One month later, after deviating from his low salt diet, his weight increased to 173 pounds and ankle edema appeared. The dose of tablets was increased to 10 mg. twice a day for five days of the week. He began to complain of abdominal cramps and a "burning taste in the mouth." He was unable to tolerate the increased dosage. He was given Mercuhydrin intramuscularly with relief of symptoms, and disappearance of his gastro-intestinal complaints.

This case also emphasizes the importance of continued subsidiary therapy, such as low-salt diet, along with the mercurial diuretics. Straying from his diet, in this instance, may have decreased the effectiveness of the diuretic drug. He also illustrates one type of toxicity seen in six of our patients. It was not severe, and decreasing the dosage or stopping the drug caused disappearance of toxic symptoms.

Case 16. This patient had been in failure four years. During the year before oral therapy he had received 40 Mercuhydrin injections. He was changed to tablets in dosage of 10 mg. three times a day, once a week. Two months later this was increased to two times a week. He continued satisfactorily for the succeeding five months, when recurrent rheumatic fever was suspected. He refused hospitalization, discontinued medication, and later died.

This case emphasizes the importance of patient cooperation. The necessity of close observation for factors other than inadequate dosage of the drug which contribute to progression of the congestive state, such as discontinuation of medication, or possible recurrence of rheumatic fever, is well illustrated.

There was no means by which one could determine beforehand which patient would be a favorable candidate for oral mercurial diuretics. Close observation of weight and changes in signs and symptoms is very important in determining the effect and adequacy of drug dosage. The most common effective dosage in this series was one tablet of 10 mg. of mercury three times a day, twice weekly three or four days apart. This could be increased to three times weekly, or be given twice a day five times weekly. We did not give the drug in daily continuous doses.

Comment

Ten years ago Batterman, DeGraff and Rose[7] published their observations on an oral mercurial diuretic, Mercupurin-theophylline. Each tablet contained the equivalent of 30 mg. of mercury. They found the most effective dosage to be two tablets daily for an average

of 19 days.[9] Successful diuresis was accomplished in 77 per cent of ambulant patients. However, toxicity occurred in 33 per cent of the same group. The most common toxic effect was digitalis intoxication following the diuresis. Gastrointestinal intolerance symptoms appeared in the form of nausea, vomiting and diarrhea. Two patients became uremic. In another study they reported 50 per cent toxicity with the same drug used in 13 patients.[8]

Derow and Wolff[12] reported "uniformly excellent results" in 11 patients, using Mercupurin tablets. Albuminuria and a variety of gastrointestinal symptoms including vomiting, bloody diarrhea, abdominal cramping and pains in gums and teeth were reported in 50 per cent of their case studies. One patient died of mercurialism. It was of interest to note that in spite of the above gastrointestinal symptoms the drug was continued, and in time the symptoms decreased or disappeared.

The interpretation of the gastrointestinal toxicity in oral mercurial therapy is confusing. Batterman and associates[9] believed it to be due to digitalis, since on decreasing or stopping the digitalis, but continuing the mercurial, the symptoms improved or disappeared. On the other hand Derow and Wolff,[12] without changing digitalis dosage, and still maintaining the oral Mercupurin, noted the same improvement in their toxic patients.

Another study of Mercupurin-theophylline was made by Vander Veer, Clark and Marshall.[13] In 34 ambulatory patients they noted that 79.4 per cent showed good results. Fourteen patients or 41 per cent showed symptoms of drug toxicity. Five showed slight albuminuria.

Studies have also been reported on Salyrgan-theophylline.[11, 14, 15, 16] Borg,[11] studying ambulatory and hospitalized patients observed good results in 71 per cent. Toxicity was found in 35 per cent. Carryer and associates,[14] using the same drug in a very brief study of hospitalized patients, reported toxicity in 22 per cent.

Shaffer and associates reported 60 to 70 per cent success in treating cardiac failure with Mercuhydrin-ascorbic acid tablets. Each tablet contained the equivalent of 19.5 mg. of mercury and they advised dosage of one to three tablets daily. Toxicity occurred in 25 per cent of the cases. It was primarily of gastrointestinal origin.

The findings in our series compare favorably with the above reports, although the comparisons cannot be absolute due to differing criteria of success among the various studies. It is of interest that Ex 1431 showed the lowest toxicity of any oral preparation. Only 6 of our 35 patients, or 14 per cent, developed toxic symptoms. The intolerance was gastrointestinal. There was no evidence of renal injury.

This relatively infrequent toxicity is probably due to the smaller amounts of mercury in this preparation. The average initial and maintenance dose was equivalent to 10 mg. of mercury three times a day, two or three times a week: a total of 60 to 100 mg. of mercury per week in divided doses. Batterman[9] and his co-workers found that 60 mg. daily for 19 days was the most effective mercury dosage. This equalled 420 mg. per week. Derow and Wolff prescribed as high as the equivalent of 600 mg. of mercury per week, and on occasion gave the parenteral preparation with it. Vander Veer[13] and his associates gave as much as 180 mg. daily for six weeks, or the total of 1260 mg. per week, in some instances.

Carryer[14] could obtain diuresis with Salyrgan tablets only if the equivalent of 150 mg. of mercury were given daily. Using the same drug, Borg[11] advises the equivalent of 180 to 270 mg. of mercury daily.

It is obvious that Ex 1431 achieves just as good results as other preparations, with less toxicity. It is our belief that Ex 1431 oral mercurial tablets are of value in the following situations and for the following purposes: (1) For the maintenance of "dry weight" and control over the symptoms of congestive failure after the initial acute phase has been treated with parenteral mercurials, along with other adjuncts of therapy. In the acute, suddenly changing, rapidly progressive phase of congestive failure the oral mercurials are too slow and unpredictable, and therefore unreliable.[1] Once the peak of the storm has levelled off the tablets can be used for interim

"maintenance therapy." (2) In some instances of early, mild, or slowly progressive congestive failure. Not infrequently this form of failure can be initially treated with oral in place of injection therapy. Our experience and that of others cited above is not in agreement with the pronouncement of Gold and his co-workers that "oral tablets rarely suffice. . . ."[3, 18]

Oral mercurials are contraindicated: (1) In the presence of uremia and renal disease. It must be remembered that often albumen and casts in the urine may be due to congestive failure itself, and mercurials would help instead of harm the congested kidney. (2) When significant gastrointestinal disease is present. (3) In sudden, rapidly changing or progressive heart failure.

Summary

Results in treatment of 35 ambulatory patients in chronic congestive heart failure with a new oral mercurial, Ex 1431, are presented.

This drug was found to replace intramuscular Mercuhydrin effectively in "maintenance therapy" of mercurial diuresis for periods from 1 month to 11 months, in 80 per cent of the patients studied.

Toxicity was observed in six patients, or in 14 per cent. Because of the relatively small amount of mercury necessary to attain diuresis, toxic reactions were less than those reported after the use of other oral mercury preparations.

Sumario Español

Mejoramiento en el uso de un agente terapéutico efectivo es conveniente especialmente cuando el método de administración se simplifica, la dosis total se reduce, la toxicidad de la droga disminuye y el costo del cuidado médico se reduce. La substitución de inyecciones parentéricas de diuréticos mercuriales por una preparación oral en pacientes ambulantes con decompensación cardiaca crónica representa un paso hacia delante en el manejo de esta clase de paciente.

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Temporary Hemiplegia from Cerebral Injection of Diodrast during Catheter Aortography

Report of Two Cases

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Brain damage manifested by convulsions, hemiplegia, or death may result whenever concentrated Diodrast is injected into the cerebral circulation. Reactions are fairly common following cerebral angiography but may follow contrast visualization of the thoracic aorta by any method. The greatest danger is in aortography when the maximum dye concentration is in the aortic arch. The reactions probably do not result from vascular spasm but from an alteration in the blood-brain barrier. It is possible to minimize the danger of reactions in aortography by observing certain simple precautions. Treatment of brain damage when it occurs, however, is not satisfactory.

BRAIN DAMAGE resulting from cerebral injection of Diodrast or related compounds is perhaps the most common complication of cerebral angiography[1] but the fact that similar grave reactions may result from contrast visualization of the aorta and its major branches is not generally appreciated. There are very few reports of such complications in the literature[2, 3] and the reasons for their occurrence are poorly understood. Since aortography and related procedures are coming into more general use, two cases of temporary hemiplegia in a series of 19 thoracic aortograms employing Diodrast are reported in detail. The method of aortography employed has been described previously.[4]

Case Reports

Case 1. A 35 year old white male administrator was admitted for evaluation of an aortic diastolic murmur noted on routine physical examination. No murmur had been noted on previous examinations and the patient had had no cardiovascular or other symptoms. There was no history of syphilis or rheumatic fever.

The physical examination was within normal limits except for a grade 2 soft blowing aortic diastolic murmur and a grade 1 apical systolic murmur. The blood pressure was 140/80.

Serologic tests for syphilis on blood and spinal fluid were negative. Hemogram, urinalysis and electrocardiogram were within normal limits. A chest roentgenogram was normal except for aortic dilatation. Fluoroscopy revealed overactive aortic pulsations. Serial blood cultures showed no growth.

It was considered that the patient probably had aortic insufficiency but the possibility of an atypical aortic coarctation or other anomaly was also entertained. Consequently, aortography by the percutaneous femoral route was carried out.

Following premedication with 15 mg. morphine sulphate and under local xylocaine a polyethylene catheter was inserted into the left femoral artery and passed under brief fluoroscopic control into the ascending aorta. There was no reaction to the intra-arterial Diodrast used for positioning the catheter which was shown at the level of the aortic valve (fig. 1*a*). It was withdrawn about 4 cm. and with the patient performing a Valsalva maneuver, 20 cc. of 70 per cent Diodrast were injected in three to four seconds and a film taken. The ascending aorta was uniformly dilated. The aortic valves showed definite regurgitation of Diodrast (fig. 1*b*). A second film was made with the patient repositioned. There was no reaction following these injections. To visualize the descending aorta better the catheter was withdrawn about 8 cm. and a third film was taken. The patient experienced marked discomfort in the left head, neck, and arm but soon said he felt all right. There was a visible flush in the left face and in the area of distribution of the left internal mammary artery. The film showed the injection to be in the mid arch with the left common carotid and left subclavian arteries densely opacified. There was no

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demonstrable abnormality (fig. 1*c*). The patient helped himself from the table but 15 minutes later a right hemiplegia developed. Fifty cubic centimeters of 50 per cent glucose were given in about 10 minutes after which the patient moved his arm but did not talk. Within 15 minutes he could move all four extremities, perform requests, and answer simple questions. Thirty minutes later there was a relapse with aphasia and almost complete right paresis. The patient made no effort to speak and would not follow simple commands. Fifty cubic centimeters of 50 per cent glucose caused no definite improvement. The temperature rose, reaching a peak of 101.2 F. in six hours and falling to normal after several days. Eight hours after the accident, lumbar puncture revealed a pressure of 220 mm. and a count of 1 lymphocyte and 12 red blood cells per cubic millimeter. A left stellate ganglion block was performed and the patient placed on papaverine and Dicumarol. By the following morning the patient was able to move his right side and could answer yes and no to questions, usually appropriately. Twelve hours later his right grip was near normal and he could say brief sentences. Speaking was a great effort and there was nominal apraxia, the patient being unable to say his name without prompting. He could read but could not understand much of what he read. A second stellate ganglion block was carried out. Improvement was progressive and in four days the patient appeared normal but felt that his speech was slow. It was learned that he was left handed.

No etiologic diagnosis could be made for the aortic dilatation and regurgitation but because the findings were similar to those of syphilitic aortitis a total course of 10,000,000 units of penicillin was given. Subsequently he returned to a very responsible job without difficulty and has shown no residual cerebral dysfunction.

This patient was in vigorous health and without cerebral disease. A total dose of 20 cc. of 70 per cent Diodrast was injected into the aortic arch and the distribution of dye in the roentgenogram indicates that not over 5 cc., somewhat diluted, could have entered the cerebral circulation. The most important contributing factor was certainly the concurrent Valsalva maneuver. This may have caused sufficient circulatory slowing to predispose the brain to damage.[5] A reasonable pathologic interpretation of the reaction is that immediately there was an increased capillary permeability with secondary cerebral edema involving the dis-

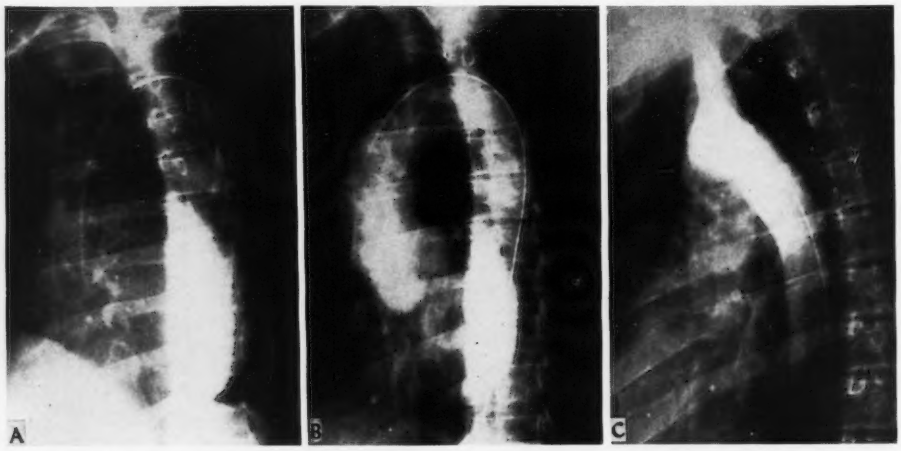

FIG. 1. Case 1. (*a*) Catheter positioning film, right posterior oblique position. The tip is at about the level of the aortic valve. Catheter I.D. 0.062 inch, O.D. 0.082 inch.

(*b*) First aortogram, right posterior oblique position with 20 cc. of 70 per cent Diodrast. The catheter tip is at some distance from the aortic valves. The ascending aorta is uniformly dilated. The aortic valves are well outlined and there is definite reflux of Diodrast into the left ventricle. No other abnormality is seen.

(*c*) Third aortogram, left posterior oblique position, with 20 cc. of 70 per cent Diodrast. The catheter has been withdrawn so that the tip lies in the distal aortic arch. The left common carotid and left subclavian arteries are densely opacified but the arch and proximal descending aorta also contain a considerable density of Diodrast. There are no demonstrable abnormalities.

tribution of the middle cerebral artery. Possibly the use of 50 per cent glucose decreased the edema for a time. At any rate the reaction became more severe and certainly went on to some type of mild hemorrhage as shown by the spinal fluid. Whether stellate blocks, papaverine, or Dicumarol exerted a beneficial effect cannot be deduced from the record.

Case 2. A 54 year old Negro man was referred to the Tumor Service by the Veterans Administration in connection with a pension application because of roentgen findings of a mediastinal mass. About 20 months before admission there had been a gradual onset of exertional dyspnea and chest pain. Seven months before admission he was treated for severe cardiac decompensation in the dispensary of the Johns Hopkins Hospital with digitalis, mercurial diuretics, and a low salt diet. Diagnoses of syphilitic aortitis, aneurysm of aorta due to syphilis, and arteriosclerotic heart disease were made and he was given a course of 6,000,000 units of penicillin. Following this the patient was essentially symptom free on decreased activity. There was a history of an untreated penile lesion at the age of 17. The remainder of the history was essentially noncontributory.

Physical examination revealed evidence of recent weight loss. The blood pressure was 144/65 and equal in the two arms. Pupils reacted normally to light and accommodation. The trachea was in the midline but there was a distinct tug. Dilated veins were present over the upper chest. The heart was grossly enlarged and the area of retromanubrial dullness was increased. There was a grade 2 blowing aortic systolic murmur. No diastolic murmur was heard. Peripheral arteries were thickened. The remaining physical findings were noncontributory.

Routine laboratory studies were within normal limits except for a quantitative Kahn test of 32 units. Multiple films of the chest showed a deformity of the barium-filled esophagus produced by a sharply demarcated mediastinal density (fig. 2*a*). Fluoroscopic study revealed pulsation of the mediastina mass. An electrocardiogram showed left axis deviation, left ventricular strain, first degree heart block, and digitalis effect. The circulation time, arm to tongue, was 32 seconds and the venous pressure right arm was 170 mm. of saline.

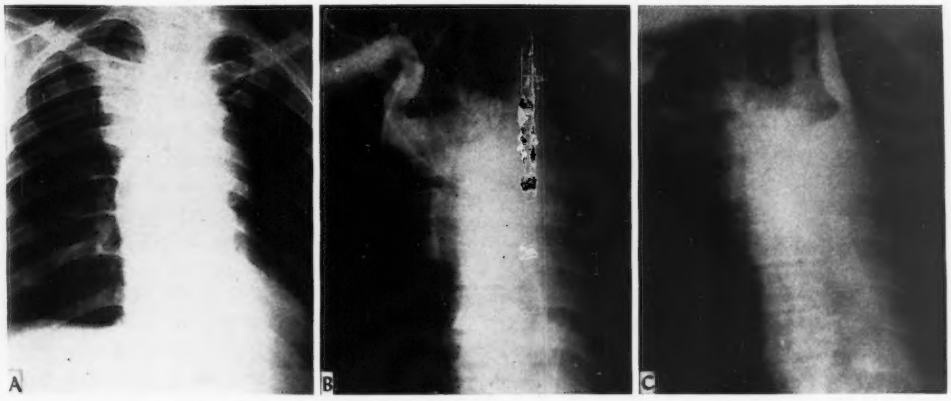

FIG. 2. Case 2. (*a*) Roentgenogram of the chest, postero-anterior projection. There is a sharply demarcated mediastinal density extending as high as the right clavicle and measuring 13 cm. in transverse diameter.

(*b*) Arteriogram, postero-anterior projection using 25 cc. of 70 per cent Diodrast, showing dense opacification of the innominate artery and its branches including the right common carotid artery. There is marked deformity of the origin of the innominate artery. The catheter pursues a grossly abnormal course. Catheter I.D. 0.053 inch, O.D. 0.085 inch.

(*c*) Aortogram, postero-anterior projection using 20 cc. of 70 per cent Diodrast. There is marked opacification of the left common carotid artery which is narrowed at its mouth. The aortic arch shadow is widened and distorted.

The patient was transferred to the Cardiovascular Clinic and an angiocardiogram was attempted. This showed only obstruction of the right subclavian vein with numerous collateral channels. Consequently, an aortogram was carried out under local anesthesia using the right percutaneous femoral route. It was not possible to pass the Diodrast filled catheter into the ascending aorta but during manipulation it entered aortic arch branches several times. A film appeared to show the tip in the arch and a roentgenogram was made during the injection of 25 cc. of 70 per cent Diodrast in about eight seconds

while the patient performed a Valsalva maneuver. Since the catheter tip was in the innominate artery (fig. 2*b*), it was then withdrawn in stages to about the center of the arch. A film showed the opaque medium largely in the left carotid. After further withdrawal a fourth film was made which also showed filling of the left common carotid artery. A total of about 110 cc. of 70 per cent Diodrast had been injected over a 90-minute period. Films revealed findings consistent with syphilitic aortitis and aneurysm of the aortic arch (fig. 2*c*). Approximately one hour after the completion of aortography there was a sudden onset of left hemiplegia accompanied by marked apprehension and subjective numbness of the left side. Fifty cubic centimeters of 50 per cent glucose were started intravenously without delay. Some function had reappeared in the left leg just prior to glucose administration and during the infusion motor function began to return in the left arm. There was no change in vital signs or electrocardiographic findings. Thirty minutes later there was only slight left sided weakness and the following morning the patient showed no residual neurological disturbance. Diagnoses at discharge were the same as those made at Johns Hopkins Hospital and the patient was referred to that institution to be followed.

The tendency of the catheter repeatedly to enter aortic arch branches indicates gross deformity of the arch region and is strongly suggestive in itself of aneurysm. Special care must be taken when the anatomic relations are so distorted in order to prevent injection of contrast material directly into a branch of the aortic arch. Although this patient had rather advanced cardiovascular disease, there was no gross evidence of cerebral involvement and the reaction is reasonably ascribable only to the Diodrast injection. There was no evidence of Diodrast sensitivity but there was ample opportunity for concentrated Diodrast to reach the right hemisphere at a time when the circulation was slowed by the Valsalva maneuver, since at least 50 cc. were injected directly into the innominate artery. There was also obvious chance for Diodrast to reach the left hemisphere under similar circumstances but this appears to have caused no trouble. It is likely that the cerebral reaction consisted only of edema. It was, however, in the right or more silent hemisphere and no spinal fluid examination was carried out to exclude hemorrhage.

Discussion

Cerebral arteriography as originally reported by Egas Moniz in 1927 employed 25 per cent sodium iodide as a contrast medium. There were frequent reactions and an appreciable mortality.[6] For this reason Thorotrast was introduced but has not been widely used, at least in this country, because of the reported late incidence of sarcoma and radiation injury.[7] It was not until the use of dilute Diodrast was popularized that this procedure became generally accepted.*

Diodrast and similar compounds are used in hypertonic solutions, 35 per cent Diodrast having roughly twice the osmotic pressure of blood. In clinical amounts there is a brief blood pressure drop[8, 9] while large doses may produce prolonged hypotension, and respiratory stimulation followed by depression.[10] Rats tolerate 3.5 Gm. per kilogram while 4.5 Gm. is a lethal dose. This compares with 3.75 Gm. and 5 Gm. respectively in mice. Dogs show no toxic effects with 1.5 Gm. per kilogram while 4 Gm. per kilogram gives a mortality of about 20 per cent.[9] The lethal dose in man is not known. Generally it is considered permissible to give single injections of about 0.5 to 1.0 Gm. per kilogram in adults which may be repeated after an interval. Such large doses are commonly used, however, only in angiocardiography.

Important human reactions appear to be related to hypersensitivity, cardiac arrhythmias, and cerebral damage. In a survey of reactions following Diodrast injection, mainly in urology, Pendergrass and his co-workers in 1942[11] reported 26 deaths in 661,800 cases. Ten of these were immediate and appeared to be on an anaphylactoid basis. The causes of the remainder were not clear. It has recently been shown that angiocardiography may bring about important electrocardiographic changes

* Diodrast is a trade name for the diethanolamine salt of 3.5 diiodo-4-pyridone-N-acetic acid. Other names include Umbradil, Dijidon, Perabrodil, Diodone, Pyelosil, and Pylumbrin. Umbradil forte is a 50 per cent solution of Umbradil with diethylamine added. Umbradil-methyl-glucamine is the methyl-glucamine salt while Ioduron is the morpholine salt. All are made up by weight volume and contain about 50 per cent iodine in firm combination.

and this toxic cardiac action may account for a few of the deaths from this procedure.[12] In this regard Helmsworth, McGuire, and Felson reported an arrhythmia and sudden death following coronary arteriography.[13]

By far the most important group of reactions are those resulting from cerebral damage. Dotter and Steinberg report 23 deaths in a series of 6,824 angiocardiograms collected by questionnaire.[9] The majority of these occurred in patients with congenital heart disease with septal defects which probably permitted concentrated Diodrast to go more or less directly to the brain. Death was generally from respiratory failure. Minor cerebral reactions to Diodrast following angiocardiography probably occur even more frequently. Gross reported two cases of jacksonian convulsions and one hemiplegia following the use of 70 per cent Diodrast in 10 patients but only one convulsion in 10 patients when 50 per cent Diodrast was employed for cerebral arteriography.[14, 15] Dyke reported a severe cerebral reaction following the use of 35 cc. of 70 per cent Diodrast for a cerebral arteriogram.[16] During the past 10 years Diodrast has generally been employed in 35 per cent solution and there have been very few reports of complications. Important papers listing no major complications include: Ingraham and Cobb, 1947, 25 cases[7]; Lindgren, 1947, 153 cases[17]; Green and Arana, 1948, 107 cases[18]; Torkildsen, 1949, 2,000 cases.[19] In 1949, however, Chusid, Robinson, and Margules-Lavergne[20] presented two cases of transient hemiplegia complicating cerebral arteriography at the New York Society of Neurosurgery and in the general discussion 21 additional similar complications following cerebral angiography with 35 per cent Diodrast were reported. Important electroencephalographic changes lasting up to 27 days occurred in Chusid's two cases. Dunsmore, Scoville, and Whitcomb in 1951[1] reported 11 cerebral complications in 147 carotid angiograms. These included three deaths, four nonfatal hemiplegias with residual dysfunction, two transient hemiplegias, and three seizures. It is apparent that brain damage following cerebral Diodrast injection is more common than has been appreciated.

It has generally been assumed on the basis of Holm's work on arterial cinematography[21] and the early paucity of findings in experimental animals[2] that vasospasm plays the major role in the causation of complications.[22] Although transient cerebral vasospasm does occur in animals under certain conditions after Diodrast injection[23] it has not been proved that it occurs in humans or that it is of sufficient degree to cause symptoms. Demel and Sgalitzer[24] reported that peripheral arteriography with 20 per cent Perabrodil (Diodrast) induced prolonged increase in the lumen of smaller arteries in animals. In actual practice visible vasodilatation with a flush resembling that of histamine is not infrequently observed in humans as in the two cases here reported. Certainly further investigation is necessary before it can be concluded that Diodrast causes cerebral arterial spasm in humans under clinical conditions and such studies are difficult because of the peculiarities of cerebral blood flow.[25] The excellent work of Bromen and Olsson with intravascular injection of the vital dye trypan blue demonstrated very clearly that the probable cause of cerebral damage to Diodrast and related compounds was a disturbance of the blood brain barrier resulting in a pathologic sequence of events including increased vascular permeability, cerebral edema, punctate hemorrhages, stasis, and infarction.[5, 23, 26] The stage of damage reached in animals depended primarily on the concentration of the contrast medium and the time that it was present in the cerebral arteries.[26] Damage, however, was greatly augmented by repeated injections of Diodrast compounds, concomitant slowing of the cerebral circulation, or prior subclinical damage with unrelated substances.[5] They also demonstrated that reactions were probably not due primarily to the increased osmotic pressure of the contrast substances alone as had been maintained earlier since it took concentrations of such substances as sodium chloride or glucose equivalent to much higher osmotic pressures to produce even minor pathological changes.[26]

Contrast visualization of the proximal aorta and its great branches in adults requires the

use of 70 per cent Diodrast and under certain circumstances considerable amounts of injection material may enter the brain. Such procedures are being used with increasing frequency yet there are very few reports of cerebral complications. Freeman and associates, in 1949[2] reported one case of temporary hemiplegia and one case of prolonged brain stem and cerebellar damage resulting from retrograde aortography via the carotid artery. A case of left hemiplegia has been reported by Bierman and co-workers, following right carotid catheterization with injection of only 11 cc. of 35 per cent Diodrast into the internal carotid artery.[3] In these cases complications may be ascribable to carotid manipulation or temporary compression as well as to the injection of Diodrast. Immediate convulsions with death after four hours occurred in a case of a 36 year old woman when an injection of 22 cc. of 70 per cent Diodrast was made into the mouth of an anomalous left innominate artery using the method of Radner.[27, 28] As in the two cases reported in the present paper this reaction may reasonably be ascribed to cerebral damage from Diodrast alone.

It is thus clear that concentrated Diodrast injected into the aortic arch or directly into the innominate, carotid, or left subclavian arteries may gain access to the brain via the vertebral or carotid arteries. Ordinarily, the relatively small volumes of Diodrast are safely diluted before they reach the brain but there is always some danger and whenever there are repeated injections or where the cerebral circulation has been slowed as by the Valsalva maneuver there is grave danger of serious reaction. For these reasons, the following precautions are strongly recommended during thoracic arteriographic procedures[4]: (1) Do not inject dye in such a manner that the maximum concentration is in the arch unless this is essential to the success of the procedure. (2) If a catheter is employed always ascertain where the tip is by a positioning film and do not have it in one of the aortic arch branches if 70 per cent Diodrast is to be used. (3) The Valsalva maneuver[2] should not be employed whenever Diodrast may directly enter the cerebral circulation. (4) After a preliminary test, apply digital carotid pressure to prevent concentrated dye from reaching the brain if an injection is made directly into the aortic arch.[13] This should probably be done also whenever a coarctation of the aorta is examined by a proximally inserted catheter as concentration of the dye in the arch region is favored by this anomaly. (5) The use of 35 per cent Diodrast is satisfactory in infants and small children and here 70 per cent Diodrast should be avoided. (6) With single film technics good pictures may frequently be obtained with as little as 10 cc. of 70 per cent Diodrast. If a rapid changer is available half of this dose may suffice. The smallest volume permitting adequate examination should be employed.

It would also appear desirable to avoid direct injection into the coronary ostia unless specific information about the coronary arteries is required. These precautions apply to all types of catheter arteriography,[4, 13, 27] retrograde arteriography,[2] and aortography by trocar[29] or needle.[30] In addition to the above measures suitable emergency drugs should be available to combat an anaphylactoid reaction, hypotension, or respiratory failure. It has been suggested also that barbiturate anesthesia[31] provides some protection against brain damage. Antihistaminic drugs do not appear to protect against reactions.[32]

There is no generally advocated method of treatment should a cerebral Diodrast reaction occur. Most therapy has been aimed at combatting arterial spasm and for this purpose vasodilators such as papaverine and tetraethylammonium chloride as well as sympathetic blocking by means of serial stellate ganglion injections have been employed.[1, 20] Procedures to combat cerebral edema, as the injection of hypertonic glucose, may be tried but their effectiveness is unknown. The use of anticoagulants would appear to have much the same rationale as their use in coronary occlusion. All methods of therapy, however, need careful evaluation in animals and a fruitful attack would appear to be by employing the vital dye technique of Bromen and Olsson[23] in statistically valid series of experimental cases. It is hoped that a truly satisfactory

inert contrast medium will eventually be forthcoming.[33]

Summary

Two cases of temporary hemiplegia immediately following thoracic aortography are reported. Seventy per cent Diodrast was employed as a contrast medium. The literature on arteriography is reviewed for similar cases. Reactions of this type may result whenever concentrated Diodrast enters the cerebral circulation and their occurrence is probably favored by repeated injections, slowing of the cerebral circulation, or preexisting pathological states. Evidence supports the contention that damage is due to alterations in the blood brain barrier rather than vascular spasm. Means of avoiding reactions and possible therapeutic measures are outlined.

Sumario Español

Daño cerebral manifestado por convulsiones, hemiplegia, o muerte puede resultar cuando Diodrast concentrado es inyectado en la circulación cerebral. Reacciones son bastante comunes consiguiente a angiocardiografía cerebral y pueden también ser consiguientes a angiocardiografía de la aorta torácica por cualquier método. El peligro más grande es en la aortografía cuando la concentración máxima del tinte se encuentra en el arco aórtico. Las reacciones probablemente no resultan debido a espasmo vascular pero si a alteración producida mediante la barrera entre el cerebro y la sangre creada por el tinte. Es posible reducir al mínimo el peligro de reacciones en aortografías observando precauciones simples. El tratamiento para el daño cerebral cuando este ocurre no es satisfactorio.

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A Quantitative Metabolic Defect in Lipid Metabolism Associated with Abnormal Serum Lipoproteins in Man

By MAX W. BIGGS, M.D., AND DAVID COLMAN, B.S.

Tritium-labeled cholesterol has been fed to a selected series of patients to demonstrate a quantitative metabolic defect in lipid metabolism in the presence of abnormal serum lipoprotein spectra. Patients with abnormal serum lipoprotein spectra carry a greater fraction of their newly absorbed cholesterol in the esterified form than do normals.

THE LIPOPROTEINS of human serum are conveniently defined and quantitated in the ultracentrifuge according to their flotation rates under carefully defined conditions.[1] Inasmuch as the concentration of certain serum lipoprotein molecules so defined (S_f 12–20; S_f 20–100*) show a positive correlation with the incidence of human atherosclerosis,[2] those factors which determine the lipoprotein spectrum of the serum in any individual become of potential importance in understanding the pathologic physiology of atherosclerosis.

A search for determining factors important in lipoprotein metabolism logically includes several varied aspects of cholesterol metabolism. The interrelationships between serum lipoprotein spectra and oral cholesterol metabolism are under investigation in this study. Labeled cholesterol has been administrated to a series of 10 patients, and it has been possible to demonstrate a quantitative metabolic defect in lipid metabolism in patients who have abnormal ultracentrifugal lipoprotein spectra.

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* Units are Svedbergs of flotation (S_f). One S_f unit equals a migration rate of 10^{-13} cm./sec./dyne/Gm. at 26 C. in a medium of sodium chloride solution of density 1.063.

Tritium-labeled cholesterol[3] has been fed to 10 selected patients: two with xanthoma tuberosum, two with xanthoma tendinosum, three with clinical atherosclerosis, and three normals. Patients with xanthomata have been used in four instances because they afford a unique opportunity to study extremes in lipoprotein spectra.[4] Patients with xanthoma tuberosum have elevated serum cholesterol values associated with an extremely abnormal ultracentrifuge pattern; the lipoprotein spectrum approaches that seen in cholesterol-fed rabbits. In xanthoma tendinosum, on the other hand, there is also a hypercholesterolemia but here the ultracentrifuge lipoprotein spectrum is of particular interest in that the hyperlipoproteinemia remains almost entirely within the S_f 0–12 class of lipoprotein molecules. The 10 patients selected then afford a sampling over a wide range of lipoprotein spectra. Besides providing a wide range of serum lipoprotein spectra the patients also provide wide variations in serum cholesterol values as well. Within the 10 patients of the group, however, there is no correlation between the level of serum cholesterol and the type of centrifuge pattern found. As a result it has been possible to evaluate independently the quantitative metabolic differences in lipid metabolism observed in the various individuals with respect to the absolute serum cholesterol level and also with respect to the concentrations of various lipoprotein molecules.

EXPERIMENTAL PROCEDURE

A single dose of tritium-labeled cholesterol, between 0.55 and 0.77 mc., was administered to each

patient at the beginning of the experiment. The cholesterol, average dose = 0.63 Gm., was dissolved in 15 cc. of warm Wesson oil and emulsified into 200 cc. of whole milk together with 60 Gm. of ice cream. After the ingestion of this labeled fatty meal, periodic blood samples were obtained, and the serum free and total cholesterol specific activities were determined. The cholesterol in each serum sample was precipitated as the digitonide which in turn was combusted for tritium activity determinations as previously described.[5] The experiment was done on an out-patient basis and the patients ate their "regular diets" at home.

Just prior to administering the tritium cholesterol a blood sample was taken for ultracentrifugal analysis of the serum lipoprotein spectrum. Three serum cholesterol determinations were made on each patient according to the method of Schoenheimer-Sperry[6] as modified by Colman.[7] These determinations were done at approximately weekly intervals usually on the serum of days 1, 7 and 14 following the start of the experiment.

Results

For the sake of clarity the experimental results are presented in graphic form in figures 1 through 10. An ultracentrifugal analysis of the lipoprotein spectrum of the serum of each patient at the beginning of the experiment tops each figure. The concentration of lipoprotein molecules, S_f 0–12, S_f 12–20, S_f 20–100 and S_f 100–400, read from each plate, is included in the legend. It should be noted that the ultracentrifuge plates were not made at the same serum concentration in each case; the fold concentration is included for each. The shaded area in frame 5 of each plate is proportional to the concentration of S_f 12–20 molecules. The shaded area in frame 2 is the area read for S_f 20–100 molecules. The concentration of S_f 0–12 molecules has been taken from frame 5; the concentration of S_f 100–400 molecules from frame 1.*

Beneath each ultracentrifuge plate is the corresponding cholesterol specific activity absorption curve for that patient. Here the free cholesterol specific activities and the total cholesterol specific activities have been plotted as a function of time in days. The abscissa is broken at the right to include specific activity determinations over a several weeks period.

Identification of the patient together with certain pertinent information such as the tritium-cholesterol dosage is included in the legend.

The serum cholesterol values are included in table 1.

Table 1.—*Serum Cholesterol Values on the 10 Patients Studied*

Patient No.	Sample No. 1		2		3		Average		Average Ratio Total Chol./ Free Chol.
	Free	Total	Free	Total	Free	Total	Free	Total	
	mg. %	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*mg. %*	
1	141	496	151	566	138	496	143	519	3.6
2	162	560	140	546	144	588	149	565	3.8
3	51	223	50	232	48	224	50	226	4.5
4	84	358	88	367	74	331	82	352	4.3
5	37	178	49	208	40	194	42	193	4.6
6	73	273	78	268	75	258	75	266	3.5
7	72	275	69	283	58	239	66	266	4.0
8	154	500	142	538	143	550	146	529	3.6
9	63	268	58	243	71	358	64	290	4.5
10	76	259	72	258	72	259	73	259	3.5

Discussion

Examination of the 10 cholesterol specific-activity absorption curves shows a quantitative difference in the way various individuals handle oral cholesterol with respect to its partition after absorption into the free and esterified pools of serum cholesterol. Patient 1, after 24 hours, shows a free serum cholesterol specific activity 2.19 times as great as the total serum

* The method of plate reading employed in this laboratory has been developed by Dr. John Gofman and will be reported in detail elsewhere.

cholesterol specific activity; while patient 10, after 24 hours, shows a free serum cholesterol specific activity only 0.52 times as great as the total serum cholesterol specific activity. The remaining eight patients lie distributed between these two extremes.

Ultracentrifugal analyses of the lipoprotein spectra of several thousands of "normal" young men and women show that the normal lipoprotein spectrum consists of a moderate or high concentration of S_f 0–12 molecules, with only low concentrations of molecules with greater flotation rates than this (S_f 12–20; S_f 20–100; S_f 100–400). In the following discussion S_f 0–12 molecules are treated as normal; S_f 12–400 molecules as abnormal.

A qualitative comparison of the cholesterol specific activity absorption curves with the ultracentrifuge plates in each case shows that those patients with a "normal or nearly normal" lipoprotein spectrum, with the bulk of their lipoprotein molecules in the S_f 0–12 class, have a cholesterol specific activity absorption curve wherein the free cholesterol specific activity is greater than the esterified cholesterol specific activity during active absorption of the tritium-cholesterol dosage. On the contrary those patients with a "moderately or grossly abnormal" lipoprotein spectrum with high concentrations of S_f 12–400 molecules do not show this relationship, but rather the abnormal centrifuge plates accompany cholesterol specific activity absorption curves wherein the free cholesterol is lower than or equal to the esterified cholesterol specific activity.

To correlate the cholesterol specific activity absorption curves against the total serum cholesterol and against the concentrations of various lipoprotein molecules it has been necessary to transpose the cholesterol specific activity absorption curves into some numeric evaluation. For this purpose the ratio of the free cholesterol specific activity over the total cholesterol specific activity at 24 hours has been used. From the qualitative characteristics of the centrifuge plates and the cholesterol specific activity absorption curves (figs. 1 to 10) it is seen that when normal molecules (S_f 0–12) predominate the free cholesterol specific activity at 24 hours is greater than the total cholesterol specific activity. When abnormal molecules predominate (S_f 12–400) the esterified cholesterol has the greater specific activity.

In table 2 the ratio of free cholesterol specific activity over total cholesterol specific activity, the ratio of normal S_f 0–12 molecules over abnormal S_f 12–400 molecules, and the total serum cholesterol values are listed for each patient. Calculation of Pearson's product-moment coefficient of correlation between the ratio of free cholesterol specific activity over total cholesterol specific activity and the ratio of normal molecules (S_f 0–12) over abnormal molecules (S_f 12–400) gives a value of +0.93 (0.765 is significant at 1 per cent level). Calculation of the same correlation coefficient for the ratio of free cholesterol specific activity over total cholesterol specific activity and the total serum cholesterol values in milligrams per 100 cc. gives a value of +0.39 which cannot be proven significant from these data.

Thus the cholesterol specific activity absorption curves during the period of active tracer-cholesterol absorption show a positive correlation with the lipoprotein spectrum; however, from the data they cannot be correlated in significant fashion with the total serum cholesterol values in the same individuals. This positive correlation of the cholesterol specific activity absorption curves with the lipoprotein spectra and the failure of a significant correlation with the total serum cholesterol is interpreted as indicating that an ultracentrifugal analysis of the serum lipoprotein spectrum evaluates a metabolic defect in lipid metabolism which may be completely independent of the total serum cholesterol values.

Warner[8] reported in his observations on the metabolism of tracer cholesterol following oral ingestion that in dogs and terminal patients the free cholesterol specific activity is greater than the esterified cholesterol specific activity during the period of active absorption. We have previously observed that rabbits do not handle oral cholesterol in similar fashion but rather show a higher cholesterol ester specific activity than free cholesterol specific activity.[9] These observations are entirely consistent inasmuch as dogs and many terminal patients

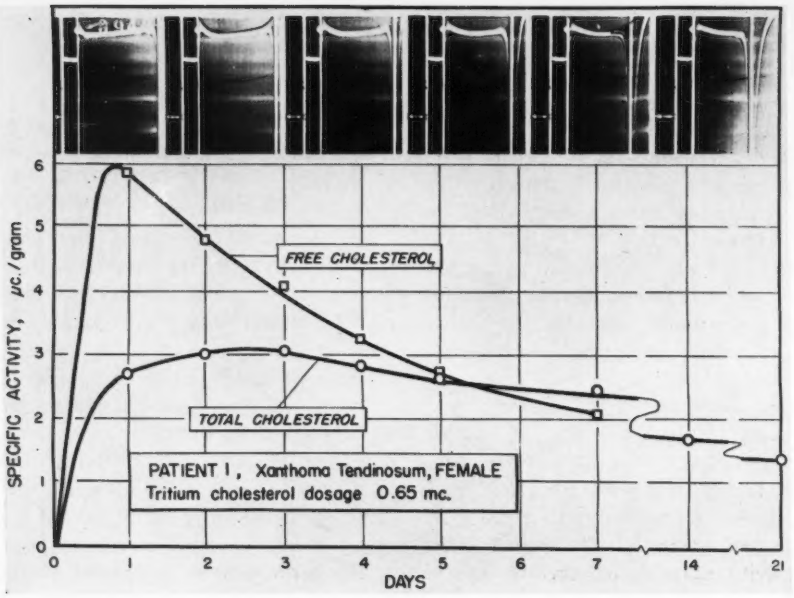

FIG. 1. Patient 1, a 52 year old female with xanthoma tendinosum of something more than 10 years duration received 0.60 Gm. of tritium cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, has been plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 974 mg. per 100 cc.; S_f 12–20 = 102 mg. per 100 cc.; S_f 20–100 = 59 mg. per 100 cc.; and S_f 100–400 = 14 mg. per 100 cc. The ultracentrifuge plate was made at a two-fold concentration.

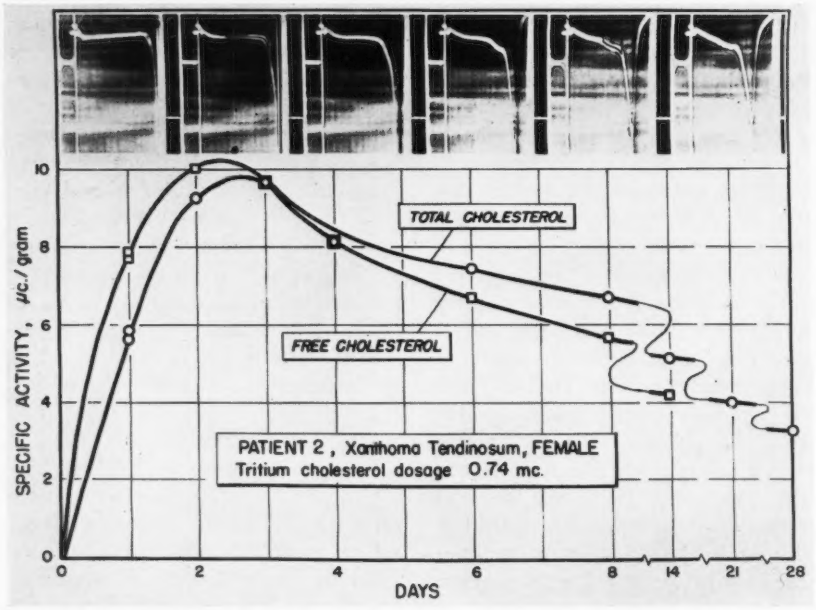

FIG. 2. Patient 2, a 51 year old female with xanthoma tendinosum of approximately 30 years duration, received 0.76 Gm. of tritium cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 966 mg. per 100 cc.; S_f 12–20 = 252 mg. per 100 cc.; S_f 20–100 = 166 mg. per 100 cc.; and S_f 100–400 = 28 mg. per 100 cc. The ultracentrifuge plate was made at a one-fold concentration.

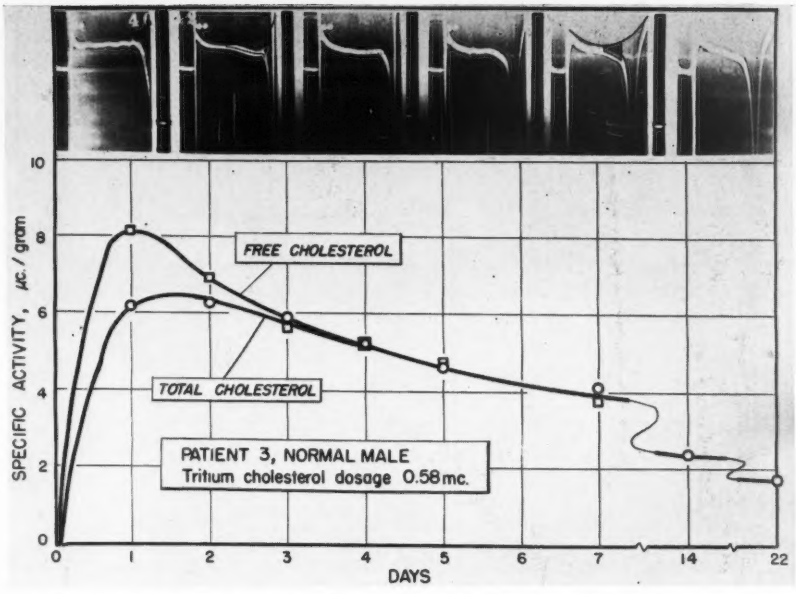

FIG. 3. Patient 3, a normal male, age 31, received 0.54 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 274 mg. per 100 cc.; S_f 12–20 = 53 mg. per 100 cc.; S_f 20–100 = 77 mg. per 100 cc.; and S_f 100–400 = 10 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

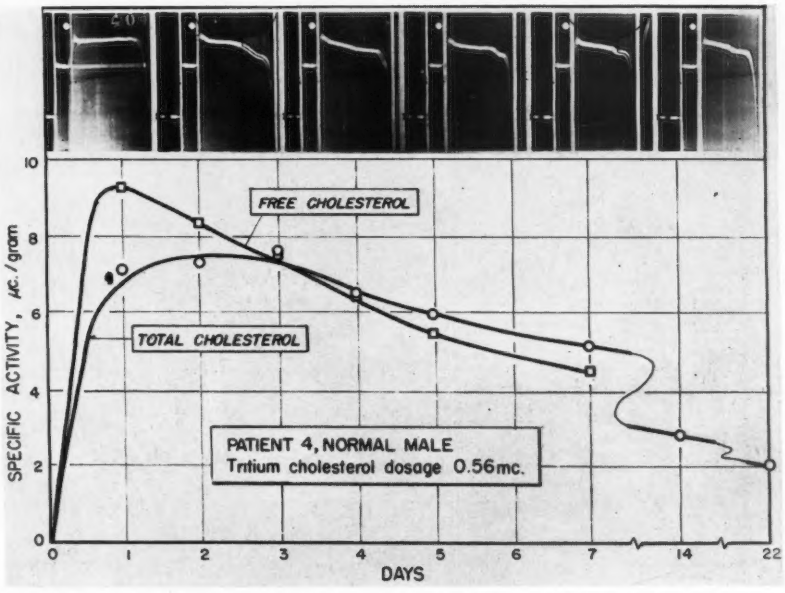

FIG. 4. Patient 4, a normal male, age 31, received 0.53 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 446 mg. per 100 cc.; S_f 12–20 = 80 mg. per 100 cc.; S_f 20–100 = 130 mg. per 100 cc.; and S_f 100–400 = 27 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

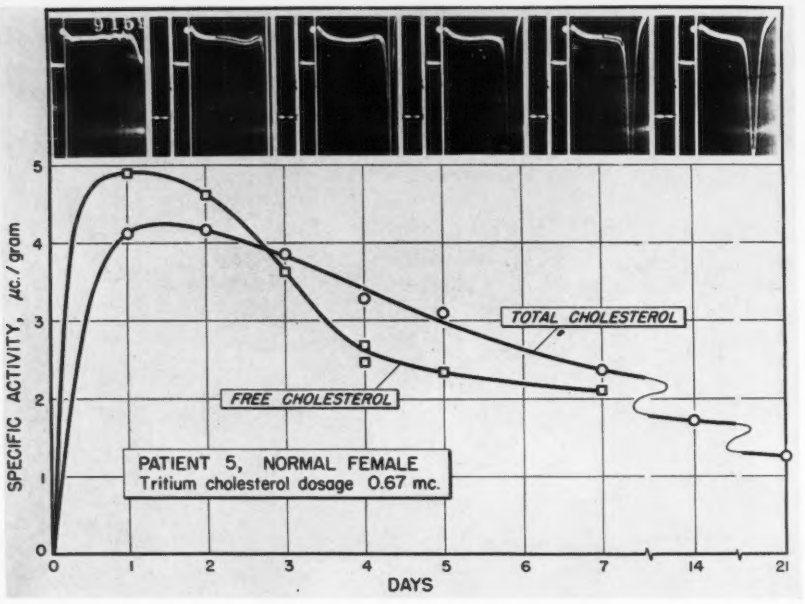

FIG. 5. Patient 5, a normal female, age 26, received 0.63 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 259 mg. per 100 cc.; S_f 12–20 = 15 mg. per 100 cc.; S_f 20–100 = 49 mg. per 100 cc.; and S_f 100–400 = 10 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

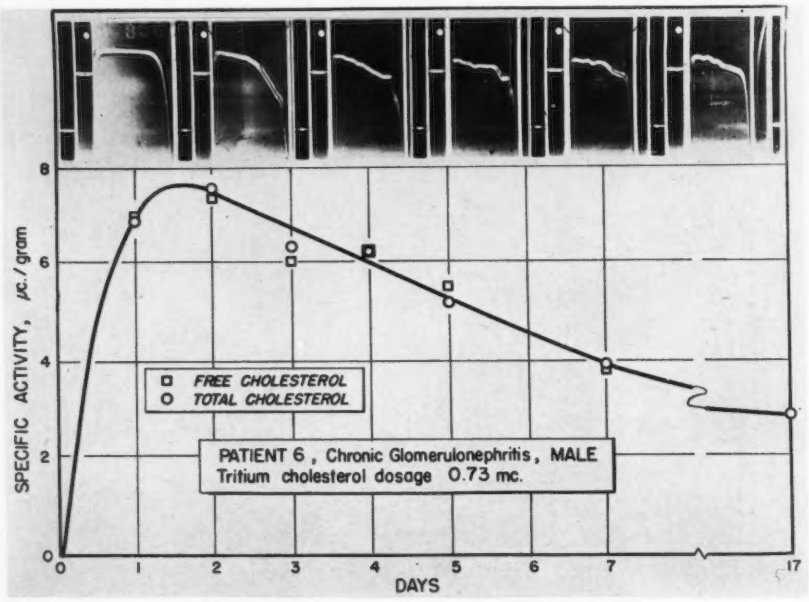

FIG. 6. Patient 6, a 41 year old male with a clinical diagnosis of atherosclerosis, hypertension and nephritis, received 0.86 Gm. of cholesterol (S.A. = 0.85 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 441 mg. per 100 cc.; S_f 12–20 = 79 mg. per 100 cc.; S_f 20–100 = 191 mg. per 100 cc.; and S_f 100–400 = 95 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

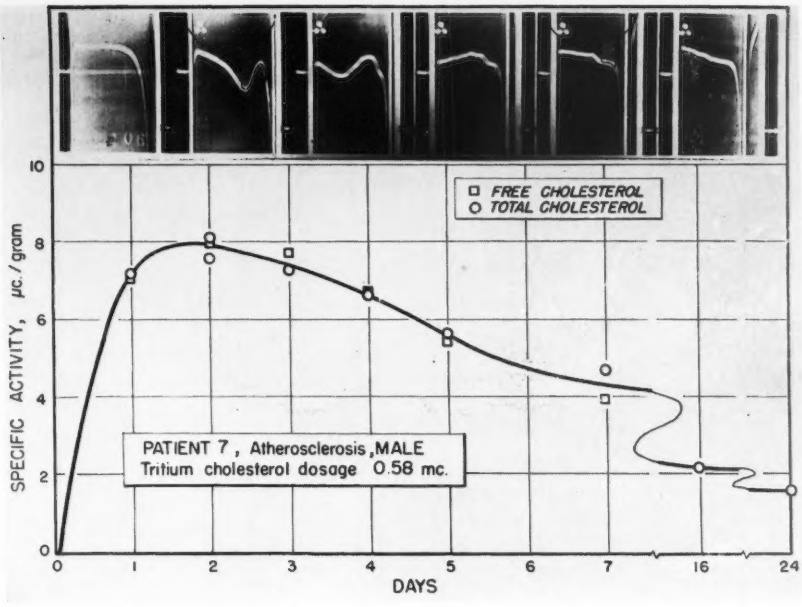

FIG. 7. Patient 7, a 42 year old male who had experienced a previous myocardial infarction, received 0.54 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 432 mg. per 100 cc.; S_f 12–20 = 61 mg. per 100 cc.; S_f 20–100 = 146 mg. per 100 cc.; and S_f 100–400 = 222 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

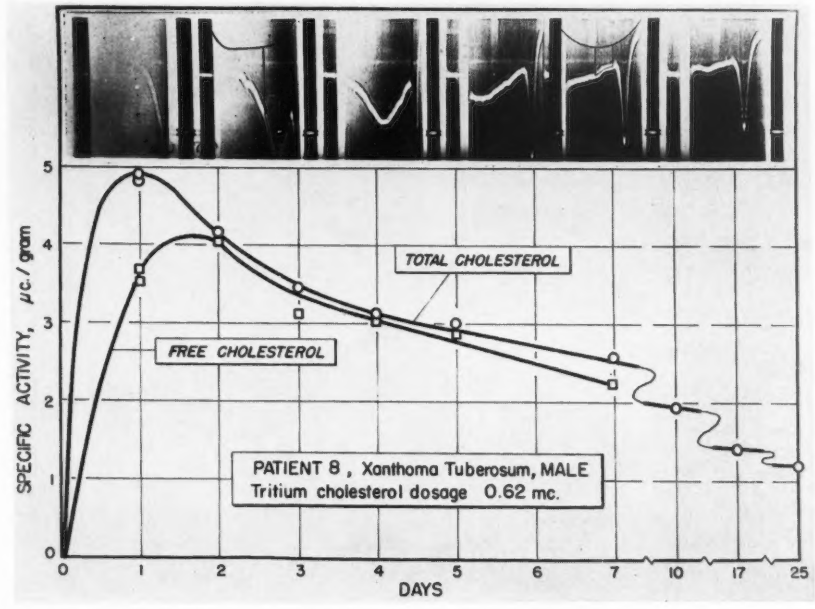

FIG. 8. Patient 8, a 42 year old male with xanthoma tuberosum of three years duration, received 0.58 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 211 mg. per 100 cc.; S_f 12–20 = 80 mg. per 100 cc.; S_f 20–100 = 493 mg. per 100 cc.; and S_f 100–400 = 254 mg. per 100 cc. The ultracentrifuge plate was made at a four-fold concentration.

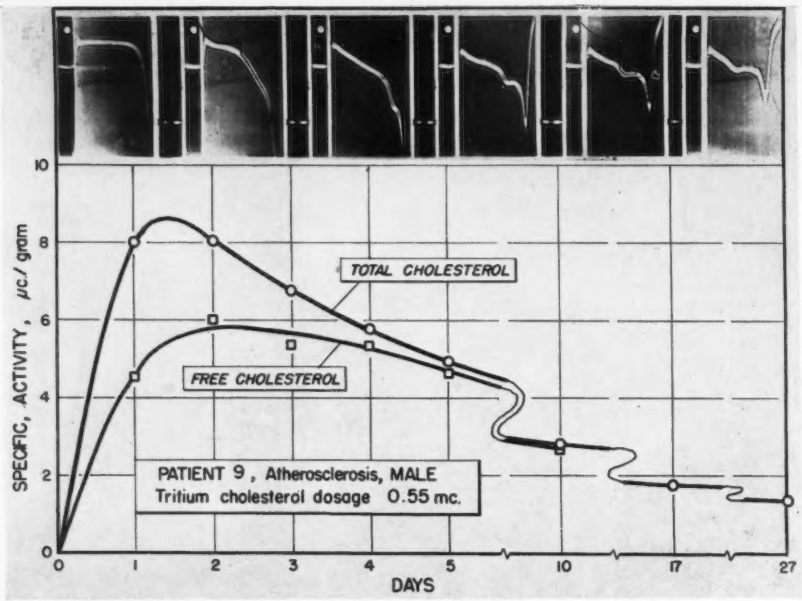

FIG. 9. Patient 9, a 42 year old male, showed a grossly abnormal ultracentrifugal lipoprotein spectrum but no demonstrable disease at this time. He received 0.51 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 178 mg. per 100 cc.; S_f 12–20 = 104 mg. per 100 cc.; S_f 20–100 = 270 mg. per 100 cc.; and S_f 100–400 = 81 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

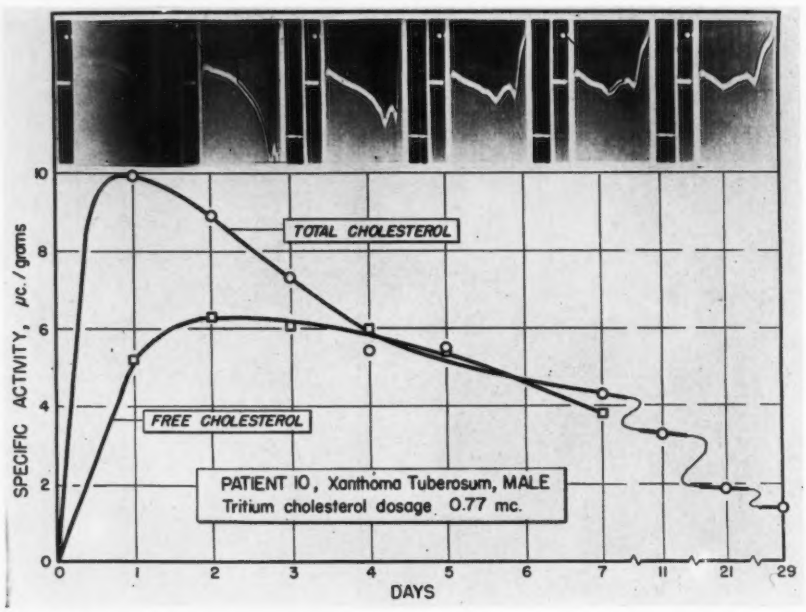

FIG. 10. Patient 10, a 34 year old male with xanthoma tuberosum of approximately three years duration, received 0.72 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 124 mg. per 100 cc.; S_f 12–20 = 99 mg. per 100 cc.; S_f 20–100 = 282 mg. per 100 cc.; and S_f 100–400 = 156 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

show what would be classified as a normal or nearly normal lipoprotein spectrum. Rabbits on the other hand show an abnormal lipoprotein picture after cholesterol feedings. Dogs do not get atherosclerosis from cholesterol feedings alone; rabbits do.

Just how applicable observations made in rabbit atherosclerosis are to the human disease is still under debate; however, as time passes, more and more observations on lipid metabolism in the rabbit are proving to have a parallelism in the "atherogenic" man. It has been demonstrated in both rabbits and man that exogenous cholesterol is only partially absorbed; however, once absorbed, that it mixes with the metabolic cholesterol pools of the serum and tissues including aorta.[9, 10] It has been demonstrated that the cholesterol fed makes up the bulk of the atheromatous cholesterol deposits in the aorta in experimental atherosclerosis.[10] Ultracentrifugal lipoprotein spectra of varying degrees of abnormality are to be found in humans and many patterns closely simulate those seen in the atherosclerotic rabbit (patients 8, 9 and 10). It has now been demonstrated that those patients with abnormal lipoprotein spectra handle oral cholesterol with respect to its partition after absorption into the serum free and esterified cholesterol pools, in an abnormal fashion; in a fashion identical with that seen in the rabbit.

TABLE 2.—*Correlation Study of Cholesterol Specific Activity Absorption Curves, Lipoprotein Molecular Spectrum, and the Total Serum Cholesterol*

Patient No.	Cholesterol specific activity absorption curves Free Chol. S.A. (μc./Gm.) Total Chol. S.A. (μc./Gm.)	Lipoprotein molecular spectrum Sf0–12 molecules (mg. %) Sf12–400 molecules (mg. %)	Total serum cholesterol (mg. %)
1	2.19	5.57	519
2	1.34	2.17	565
3	1.32	1.97	226
4	1.30	1.89	352
5	1.20	3.50	193
6	1.00	1.21	266
7	1.00	1.01	266
8	0.77	0.26	529
9	0.56	0.39	290
10	0.52	0.23	259

At this point it must be emphasized that the fundamental abnormality producing the variations in the cholesterol specific activity absorption curves observed in the patients in this study remains obscure. The problem assuredly concerns cholesterol ester metabolism, but whether the defect is in the metabolism of esterified cholesterol as a unit (that is, altered cholesterol esterase activity), or in the metabolism of one of its component parts, cholesterol and/or fatty acid, is not known. That the defect in metabolism involves cholesterol plus fatty acid in an esterified form is of additional interest in view of the fact that dietary alteration of the serum lipoprotein spectrum is most effective upon co-reduction of fat and cholesterol in the diet.

Until the various fundamental aspects of lipid metabolism are clarified and a more direct attack on the problem can be made, the bulk of evidence at hand supports the belief that judicious control of dietary fat and cholesterol as a prophylactic measure in patients with abnormal lipoprotein spectra is worth while. Such treatment would appear particularly indicated in patients such as 8, 9 and 10.

Finally it may be added that the data adds further evidence to that of McGinley and Gofman[4] that the diseases classified as xanthoma tuberosum and xanthoma tendinosum, although they have a hyperlipoproteinemia in common, probably are caused by entirely different fundamental metabolic defects.

SUMMARY

Tritium-labeled cholesterol has been used in a selected series of patients to demonstrate a quantitative metabolic defect in lipid metabolism in the presence of abnormal serum lipoprotein spectra. This metabolic defect involves the partition of oral cholesterol into the free and esterified cholesterol pools of the serum. Patients with abnormal serum lipoprotein spectra carry a greater proportion of their newly absorbed cholesterol in the esterified form than do normals.

The different cholesterol specific activity absorption curves found correlate with the

serum lipoprotein distribution as demonstrated with the ultracentrifuge; but the absorption curves do not correlate with the total serum cholesterol values found. Thus ultracentrifugal analysis of the serum lipoproteins measures a metabolic defect in lipid metabolism which can be independent of the total serum cholesterol present.

Past observations made in rabbits and dogs are consistent with the present observations in man. Cholesterol fed rabbits have abnormal cholesterol specific activity absorption curves and abnormal lipoprotein spectra. Cholesterol fed dogs have a normal absorption curve associated with a normal lipoprotein spectrum. Rabbits become atherosclerotic on cholesterol feedings alone; dogs do not.

This study appears to implicate dietary fat and cholesterol as a secondary factor in atherogenesis more strongly than before.

Acknowledgment

The authors wish to acknowledge their indebtedness to Dr. John Gofman who aided this research immeasurably with encouraging and constructive criticism. They are particularly in his debt for his careful analyses of the ultracentrifuge data.

Sumario Español

Colesterol rotulado con tritium se le ha administrado por via oral a una serie de pacientes seleccionados para demostrar un defecto cuantitativo metabólico en la presencia de espectros anormales de las lipoproteínas del suero. Pacientes con espectros anormales de las lipoproteínas del suero cargan una fracción mayor del colesterol absorbido recientemente en la forma esterificada que los sujetos normales.

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A Spatial Vector Analyzer for the Conventional Electrocardiogram

By Ernst Simonson, M.D., with the technical assistance of Jack Ross

Present methods of spatial vector analysis are descriptive rather than quantitative, or require lengthy calculations. With the spatial vector analyzer, the spatial vector is constructed from the conventional electrocardiogram, with only minor modifications of electrocardiographic routine. The method is simple, can be applied to mean and instantaneous vectors, and a quantitative characterization of any vector in terms of a horizontal angle, vertical angle, and magnitude can be obtained in about three minutes. It may be expected that the description of any deflection in simple, quantitative terms will improve the electrocardiographic interpretation by eliminating distortion resulting from the limitation to one (frontal) plane.

DURING recent years the spatial aspects of electrocardiography have found increasing consideration. Electronic apparatus to record the vectorcardiogram in three planes is now being used in several laboratories. However, the method is far from standardized, and the analysis, so far, has been descriptive rather than quantitative.[1-4] The main direction of the QRS and T loops of individual patients have been measured in a frontal, sagittal and horizontal plane,[5-7] but this method of presentation still necessitates a mental synthesis. In most of his work, Grant[8-10] is satisfied to arrive at a qualitative estimate of the direction of the mean QRS, S-T, and T vectors, but in another communication[11] he gives a quantitative method for the calculation of spatial vectors, using Wilson's tetrahedron[12] as reference. However, the calculations are too complicated to be used for a large material and especially in clinical routine.

The method described in this communication will allow one to construct the direction and magnitude of spatial vectors, using the routine electrocardiographic procedure with only minor modifications. It is sufficiently simple to be used in clinical routine.

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Principle

The Einthoven triangle represents a frontal plane which divides the body into an anterior and posterior half. The vector measurements by means of the original Einthoven triangle or in Bayley's modification[13] will give the correct values only if the vectors are in that frontal plane. If the vectors are directed posteriorly or anteriorly, the projection on the frontal plane will be foreshortened by a predictable amount if the direction in the horizontal plane is known. The data obtained from the standard leads show the foreshortened vectors in the frontal plane.* The position and magnitude of the vector in space can be obtained from the direction of the projections in the horizontal and frontal planes and the magnitude of either of these projections. For this determination of magnitude we use the frontal plane, that is, the distant leads I and III, thus obviating any estimate of distance between the precordial leads and the heart, as in Duchosal and Grosgurin's[15] or Schaefer's[16] approach.

In Bayley's diagram, the standard leads are kept parallel to the sides of the original Einthoven triangle, but displaced so as to pass through the center; for instance, lead I goes horizontally through the center. Based on this diagram, a horizontal plane and a frontal plane,

* The factor of distortion was experimentally approached by Fahr and Weber[14] in 1916.

both passing through the center of the heart, intersect in a transverse line from left to right through the center and this line of intercept is actually lead I. Therefore, lead I is common for both the frontal and the horizontal planes and the values in lead I can be used to correlate the measurements in these two planes. This operation amounts to a definition of the location of the frontal plane to which the measurements in lead I refer. The position of the end point of the vector in that frontal plane can then be found from leads I and III by means of a procedure which is not too different from Einthoven's.

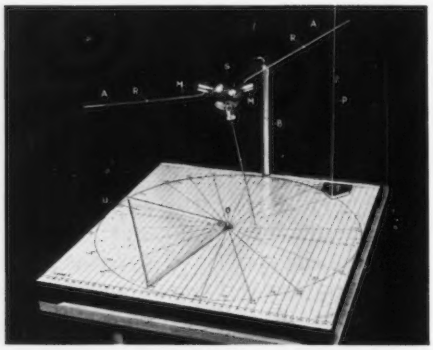


FIG. 1. Photograph of vector analyzer. *A*—vector rods; *R*—ring marks; *M*—magnets; *S*—metal sphere with center *C*; *B*—stand; *U*—rectangular ruler; *O*—central pivot rod; *P*—movable rod on triangular base *F*.

APPARATUS

The apparatus (fig. 1) consists of a baseboard, representing the horizontal plane (and used for the determination of the direction of the vector in the horizontal plane), and a metal sphere (*S*), 21 units (10.5 inches) above the baseboard, representing the center of the heart.* The metal sphere *S* (a ball bearing 2.5 inches in diameter) is held by means of a rectangular stand *B* which is ordinarily fixed to the −90 degree point (midposterior) in the horizontal plane (figs. 1, 2). An alternative fixation point is provided at the ±180 degree point (right-lateral) in order to make all possible spatial vectors accessible for measurement.

The vectors are represented by rods *A* ("vector rods") mounted on General Electric Alnico magnets 4Y13P4.* The magnets were provided with shoes which were machined to fit the surface of the metal sphere (*S*). Three vector rods (*A*) with magnets (*M*) are shown in figure 1. Some of the rods are bent in such a way that their prolongation passes through the center *C* of the sphere *S*. This makes it possible to measure any angle, however small, between spatial vectors. The magnetic properties of the Alnico magnets are excellent; with the fitted shoes they slide easily on the polished spherical surface but hold firmly to any location upon which they are placed. The length of the rods is 20 units† from the center C, and they have movable ring marks (*R*).

Horizontal Plate

The horizontal plane is a circle representing the surface of the chest at the fifth intercostal level, with the lead positions and half marks between given in terms of angles in respect to the center of the heart (fig. 2). The transverse line through the center is defined as zero (left) to ±180 degrees (right), and the midsagittal line as +90 degrees (anterior) to −90 degrees (posterior); "right" and "left" refer to the chest of the subject.

Lead I is shown in figure 2 as a transverse line through the center of the horizontal plane and a parallel as the baseline, with 20 positive units to the left and 20 negative units† to the right. The projections from lead I are marked as heavy lines (full units) and thin lines (½ units).

The construction of the horizontal plane includes a correction for the asymmetric position of the heart which was made on the basis of measurements from chest plates of 72 normal, middle-aged men,‡ and from careful consideration of cross-sectional anatomy.[17] [18] There is some experimental evidence that the arbitrarily defined mean anatomic center must be quite close to the mean electrical center.[19]

In the center of the horizontal plane is a short rod *O* of a height of 1 unit, so that its peak is 20 units from the center *C*. Rod *O* serves two purposes: as a pivot for the rectangular ruler *U*, and for the measurement of the vertical angle *V*. Since the peak of *O* and the end of the rods *A* are 20 units from the center of the sphere, the vertical angle *V*

* Since the baseboard represents the horizontal plane at the fifth intercostal space, it would appear logical to place it at the level of the sphere *S*. This would conform to Bayley's diagram. The reason for the downward displacement is purely technical. The downward displacement of the horizontal level is corrected in the construction of the vectors.

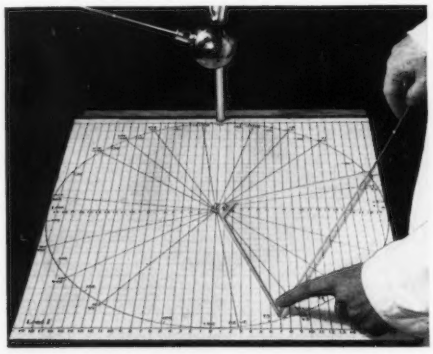
* We wish to thank Mr. W. K. Wiscomb, Carboloy, General Electric Co., Chicago, Ill., for his kind cooperation in this matter.

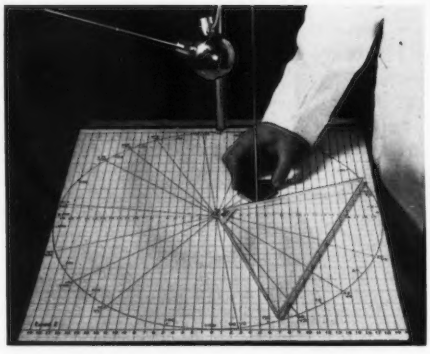
† The units represent standardized mm. deflections, or their simple multiples or fractions.

‡ We are indebted to Dr. Carleton B. Chapman for these measurements.

is measured as distance between these two points and converted into degrees by means of a special ruler (fig. 3c). The angle between two spatial vectors is measured with the same ruler as distance between the ends of the rods *A*. Since a unit equals ½ inch, the area of the horizontal plane is 20 by 20 inches.

The *rectangular ruler U* is made of transparent plastic (plexiglass) as shown in the photographs (figs. 1 to 3). The movable *vertical rod P* is fastened at the apex of a triangular base *F*, made of metal. The length of rod *P* is 30 units (15.5 inches) which is sufficient for the large majority of measurements.





A longer rod is provided for vectors with an unusually large vertical angle V.

As further auxiliary equipment, a set of straight rulers for measurement of the magnitude of the vectors, and for reading the angles directly from the distance between the end points of the vector rods (figs. 2 and 3), and a chart for determination of the vector in the frontal plane (fig. 4) are provided. The scale of the ruler which is used to measure the length of the vectors is adjusted to include the radius of the sphere *S* so that readings are obtained from the center of the sphere to the end of the vector.

Procedure (Operation and Principle)

Determination of the Direction in the Horizontal Plane (fig. 2a)

If the potential in any point of the chest surface is zero or equiphasic, the vector will project vertically (at a 90 degree angle) from a line connecting the center and this point in the direction of positivity. Therefore, the direction of the vector in the horizontal plane can be

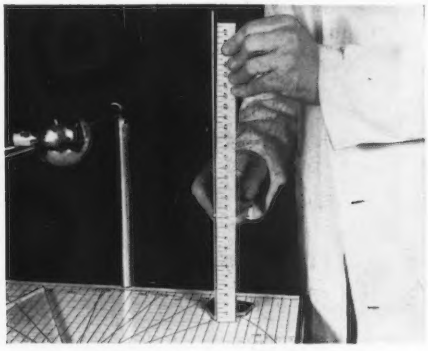


Fig. 2*a* (*top left*). Measurement of horizontal angle (*H*). For description, see text.

Fig. 2*b* (*top right*). Determination of the vector end point in the frontal plane. For description, see text.

Fig. 2*c* (*bottom*). Determination of intercept between frontal and horizontal plane. For description, see text.

determined by finding the point of zero or equiphasic potentials, using the rectangular ruler for reading the angle of the vector in the horizontal plane (H). The most probable location for the point of equiphasic or zero potentials is determined from the direction of the deflections in adjacent chest leads for both the QRS complex and T wave. In the case of the T wave the magnitude relative to the QRS deflection is also taken into consideration. One edge of the rectangular ruler is put on this point

and the angle is read at the other (reading) edge on the circular scale. (See fig. 2*a*.) The reading edge should point to the positive region of the deflection.

Determination of the Vector End Point in the Frontal Plane (fig. 2b)

It will be remembered that the center of the sphere is placed 21 units (= 10.5 inches) above the base board. We therefore determine the position of the vector end point in the frontal plane as elevation (L) above the horizontal plane, and this operation corrects also for the displacement. For this operation, a special chart is used. This chart is shown in figure 4 and represents the frontal plane, with lead I as abscissa, lead III as the oblique heavy line, and the ordinates as the height on the movable rod *P*. The midpoint *O* of lead III is 21 units above the abscissa, corresponding to the height of the center in the actual model. The heavier lines represent full units, with short lines marking half units. The thin lines mark $\frac{1}{5}$ units on the abscissa and ordinate. First, the intercept of vertical projections from leads I and III is obtained, and the height on *P* is then read as a transverse projection from this intercept on the ordinate. Figure 2*b* shows the setting of the ring mark on *P* according to the reading on the chart figure 4. The size of the chart is 16 by 16 inches, mounted on Masonite, but a size of 7.5 by 7.5 inches was also found to be quite adequate. A similar chart has been prepared for leads I and II.

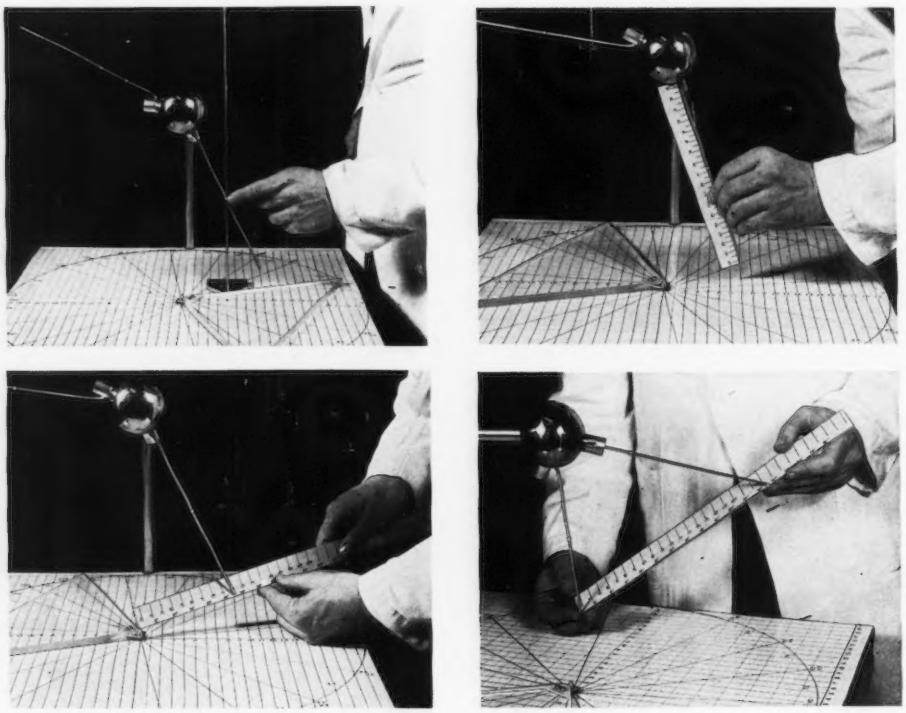


FIG. 3*a* (*top left*). Location of spatial vector. For description, see text.
FIG. 3*b* (*top right*). Measurement of the magnitude of the vector. For description, see text.
FIG. 3*c* (*bottom left*). Measurement of the vertical angle (V). For description, see text.
FIG. 3*d* (*bottom right*). Measurement of the spatial angle between vectors (dA). For description, see text.

Determination of Intercept Between Frontal and Horizontal Plane (fig. 2c)

Since the values of the deflection in lead I are foreshortened by an amount predictable from cos H (angle in the horizontal plane), the value in lead I is used to find the correction location for that frontal plane to which the values in lead I refer. This is done by finding the intercept between the direction of the vector and the projection from lead I in the horizontal plane.

Rod P is placed on the point of the abscissa corresponding to the value in lead I, and moved along the designated ordinate to the reading edge of the 90 degree ruler (fig. 2c). This point of contact is the geometric location for the intercept between the horizontal and the frontal plane. Rod P now lies in the frontal plane to which the value in lead I refers, and the ring mark on P (fig. 2b) is the end point of the spatial vector.

Spatial QRS Vector (fig. 3a, b, c)

The magnet with the vector rod A is slid on the surface of the sphere to contact the ring mark on P. The ring mark on A is set opposite this point as indicated by the left forefinger shown in figure 3a. The magnitude of the vector (Mag) is measured as distance from center to ring mark (fig. 3b) by means of a straight ruler set along the vector rod A. The vertical angle V is measured as distance between the end of vector rod A and peak of O, both having the same distance from the center (20 units). The

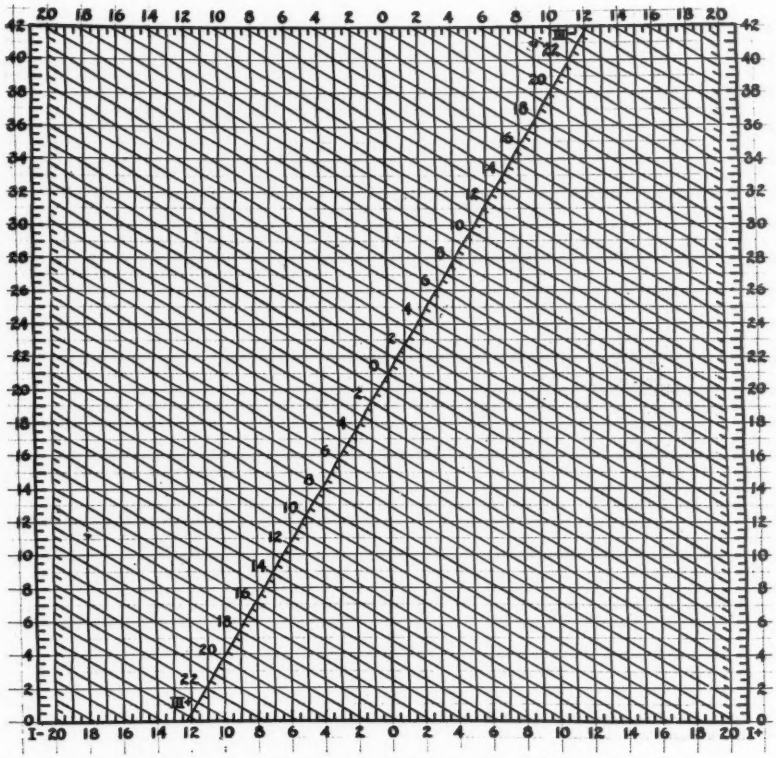


FIG. 4. Chart for determination of the elevation of the vector end point above the horizontal plane. The abscissa represents lead I, and the oblique heavy line represents lead III. A parallel to the abscissa through the zero point of lead III would reproduce Bayley's diagram, except the omission of lead II. For the use of the chart see the text.

angle can be read directly on the ruler (fig. 3*c*). The spatial angle (dA) between two vectors is also measured in a similar way, as distance between the ends of the two vector rods (fig. 3*d*).

The method can be applied for the determination of instantaneous as well as mean vectors of the P, QRS, S-T, and T deflections, as well

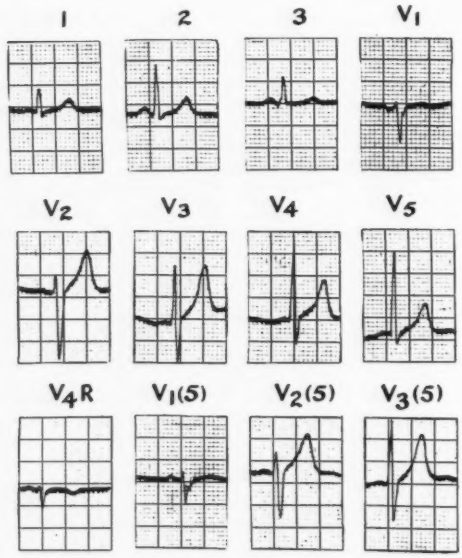


FIG. 5. Normal electrocardiogram (No. 302) with precordial leads V_1 to V_3 taken at the conventional lead positions (rows 1 and 2), and at the fifth intercostal level (row 3). For conventional V_1 to V_3, the mean QRS vector is H° = −28°, V° = 31°, Mag = 11.2 mm., and for $V_1(5)$ to $V_3(5)$: H° = −19°, V° = 29°, Mag = 10.5 mm. The mean T vector for V_1 to V_3 is H° = +28°, V° = 53°, Mag = 3.5 mm., and for $V_1(5)$ to $V_3(5)$ H° = +33°, V° = 54°, Mag = 3.9 mm.; dA° is 41° and 43°, respectively.

as of areas of the ventricular gradient. Since the magnitude of these items differs greatly, the calibration is given in 20 arbitrary units on each scale. If the value of any item is too large or too small to fit into the scale, it can be divided or multiplied. This does not change the direction of the vectors, but, of course, in order to obtain the correct magnitude of the vector, the reverse mathematical calculation is necessary.

Measurements, Definition of Direction and Signs

Each vector is characterized by two angles (horizontal and vertical), and by its magnitude. The horizontal angle (H) is read directly on the horizontal plane by means of the rectangular ruler *U*, as described before. The 90 degree ruler has to be placed in such a way that the arm for the reading points to the positive deflection.

The verticle angle is measured as distance between the end of the vector rod and peak of *O*, thus representing the angle between the vector and a vertical projection from the center *C* to the horizontal plane.

While the horizontal angle corresponds to the azimuth, the vertical angle differs from the "elevation" in analytic geometry. The Einthoven definition of α as the angle between the vector and a horizontal line through the center is actually closer to the definition of "elevation," except that positive values for α would correspond to a "depression," and negative values to an "elevation," which would be confusing. Our definition of the vertical angle V has the advantage of a very simple procedure of measurement; it could be easily expressed as positive or negative elevation in terms of V − 90 degrees.

The direction of the spatial angle between two vectors (dA degrees) viewed from above is defined as positive when the second one is in clockwise rotation from the first one, and as negative when in counter-clockwise rotation in respect to the horizontal plane. The sequence of "first" and "second" corresponds to their sequence in the heart cycle.

Example (fig. 5) of Measurement of the Mean QRS and T Vector

Step 1: Measurement of the Horizontal Angle H (fig. 2a). For the determination of the horizontal angle, the tracings from the fifth intercostal level are used (third row, fig. 5). In V_2 the S wave, and in V_3 the R wave are the largest QRS deflections so that the location for an equiphasic QRS is between V_2 and V_3 but somewhat closer to V_3. One edge of the rectangular plexiglass ruler is placed on the location indicated by the left forefinger (fig. 2*a*) and the estimated horizontal angle read at the other

edge of the ruler is −19 degrees as shown by the pointer (fig. 2*a*). The ruler is left in this position.

Step 2: Determination of Height on Vertical Rod P (fig. 2b). The mean QRS deflections, corrected for standardization, are 5.0 and 5.9 in leads I and III respectively, and those of the T wave are +2.5 and +0.7, respectively. From the chart of figure 4 the height on rod *P* is found to be 11.2 for QRS and 18.8 for T. The ring mark 11.2 on the rod *P* is set by means of a ruler (inches in decimals). The right forefinger (fig. 2*b*) points to the ring mark in this position.

Step 3: Intercept between Frontal and Horizontal Plane (fig. 2c). Rod *P* is put on the value of QRS in lead I (5.0) and approached on this line to contact the edge of the 90 degree ruler. The ring mark on *P* is now the end point of the spatial QRS vector.

Step 4: Spatial QRS Vector (fig. 3a). The magnet with the vector rod *A* is slid on the surface of the sphere to contact the ring mark on *P*. The ring mark on *A* is set opposite this point, as shown by the left forefinger.

Step 5: The Magnitude (Mag) of the Vector (fig. 3b). The magnitude of the vector is measured by means of a straight ruler, set along the vector rod *A*, as distance from center to ring mark. In this example, a value of 10.7 mm. is obtained.

Step 6: The Vertical Angle V (fig. 3c). The vertical angle V is measured as distance between the end of vector rod *A* and peak of *O*. The value is 28 degrees.

Step 7: Angle between Spatial QRS and T Vector (fig. 3d). The spatial vector for the T wave is measured in a similar way (not reproduced in figures), with the following values obtained: H = +43 degrees; V = 69 degrees; Mag = 3.4. In figure 3*d* the T vector is shown as the upper vector rod, but taken from another angle. The angle between the QRS and T vector is measured as distance between the end points of the vector rods, converted into degrees. A value of +63 degrees is obtained. The determination of the mean QRS and T vectors resulting in seven items, can be made in approximately five or six minutes.*

* For values of angle H between 80 degrees and 100 degrees the range of lead I is limited to 2.5 units or less. While such values could be arrived at through division of the orginal values, it decreases the accuracy of the measurement. Therefore, an extension of 18 units is provided for the horizontal plane. The intercept (step 3) is simply obtained by putting a straight ruler on the reading of lead I, and another straight ruler on the reading edge of the rectangular ruler as its prolongation. A magnet with a vector arm of 36 instead of 20 units is also provided. Since this auxiliary procedure is necessary only in rare instances, it has not been made a regular part of the apparatus and is not shown in the figures.

Error of Measurement

The error of the determination of spatial vectors includes the error of measurement of the deflections in lead I and III. This error was calculated on the basis of independent repeat measurements of the same tracings[20] and is quite small.

Table 1 shows the error of independent repeat measurements of the vectors in the same tracings of 30 normal men by two experimenters in terms of means and standard deviations. The probable error of the determination of spatial angles, calculated for 90 per cent expectancy, is about 5 degrees, which seems to be quite satisfactory. Also, the error of the measurement of the magnitude of vectors (about 1 mm. for QRS and 0.6 mm. for the T wave) is not large.

Effect of the Horizontal Level of Anterior Precordial Leads

The precordial leads V_1 and V_2 are taken at the fourth intercostal level, and V_4 to V_6 at the fifth intercostal level. For vector analysis all precordial leads should be taken at the same (fifth) level. Since the T wave as well as QRS complex become more inverted at a higher level, the horizontal angle as measured at the conventional lead positions is usually rotated too far to the left as shown in the example of figure 5. In 30 normal men, the conventional V_1 to V_3 were taken together with leads in the same vertical lines at the fifth intercostal level $V_1(5)$ to $V_3(5)$. The mean difference of angle H was about 6.5 degrees for the QRS as well as the mean T vector. This difference was statistically highly significant but the standard deviation was too large to suggest a standard correction for the individual tracings. Therefore,

all leads should be taken at the fifth level. However, if such leads are not available, the error is probably not too large to invalidate the measurements completely, and this is especially true for V and Mag which change but little. It is understood, of course, that an error will occur only when the zero point of a deflection is between V_{4R} and V_3. It is necessary, however, in all cases with positive T waves in V_1 to V_6 to go farther to the right (normal persons) or left (some abnormal conditions) in order to obtain good approximation of the general order of values and normal interindividual variability. These values are compared to six individual values of patients with various lesions. How far each patient is representative for any specific lesion is left open, but the tremendous differences between patients and the normal values, and between the various lesions is obvious. This, of course, is not surprising since the electrocardiograms are grossly abnormal. However, table 2 shows that spatial vector analysis will

TABLE 1.—*Means, Mean Differences* (Δ) *with Standard Deviations* (*S.D.*) *of Independent Duplicate Measurements of the Horizontal Angle* (*H*), *the Vertical Angle* (*V*), *the Magnitude* (*M*) *of the QRS and T Vector, and of the Spatial Angle* (*dA*) *between QRS and T Vector, in 30 Normal Men*

	QRS			T Wave			dA°
	H°	V°	M	H°	V°	M	
			mm.			*mm.*	
Mean, 1st meas.	−29.23	+45.03	10.98	+32.56	+61.37	3.23	49.37
Difference between 2 meas.							
Δ Mean	1.06	0.53	0.15	0.17	0.57	0.15	1.23
S. D.	2.42	2.60	0.50	2.15	2.21	0.3	2.55

TABLE 2.—*Spatial Mean QRS and T Vectors in a Group of 44 Normal Middle-Aged Men as Compared with Individual Values of Six Patients with Various Types of Pathology*

Subject(s)	Categ.	QRS			T			dA°
		H°	V°	M	H°	V°	M	
				mm.			*mm.*	
44	Normal Means:	−23.6	46.3	10.5	+37.9	64.3	3.3	+49.8
	Normal S. D.:	13.3	6.7	2.3	9.1	16.3	1.2	13.3
Koc	L. Ventr. Strain	−65	93	21.0	+100	47	2.7	−108
Flo	L. Ventr. Ischemia	−44	117	24.8	+170	77	4.7	−147
Mat	L.B.B.B.	−63	108	25.0	+120	89	4.5	+93
Lyo	Ant. Infarct	−15	38	18.8	+171	83	1.7	−120
Slo	Ant. Infarct	−51	37	7.4	+124	125	2.2	−126
Cla	Lat. Infarct	+130	113	7.6	+124	90	2.3	−23

the isoelectric location. In our material of 300 normal-aged men, in about 70 per cent leads to the right of V_1(5), and in about 10 per cent leads to the right of V_{4R} were taken in order to include the transitional point for the T wave.

Some Preliminary Results

The means and standard deviations of the mean QRS and T vectors in 46 normal men were calculated and are shown in the first two rows of table 2. While the material is too small for calculation of normal standards, it is considered to be large enough to give a fairly differentiate in a quantitative and specific way between normal and abnormal, and between various lesions.

Limitations

While there is reason to believe that the spatial vector analysis will be applicable in the majority of normal and abnormal electrocardiograms,[1–4, 8–10, 15, 16, 19, 21–23] in some cases local patterns might interfere and produce inconsistencies between the values of the frontal and horizontal planes. Although local patterns are not accessible to a precise vector analysis, the discrepancies allow a statement as to their

existence and a semiquantitative characterization of their importance.

If the direction of the vectorial forces is perpendicular to the frontal plane (that is, if H = ±90 degrees), it ceases to be representative for the electrical events. Therefore, the error of measurement increases if H approaches ±90 degrees. A partial compensation is obtained by elongation of the horizontal plane, as described in the footnote on page 409.

The definition of a mean QRS and T vector is not precise because of phase differences in the different leads. Determination of instantaneous vectors, therefore, will be more accurate than that of mean vectors, which were used for illustration of the method, but require two or three channel electrocardiographs. For determination of instantaneous vectors, only zero potentials are used for the location of the transition point.

The error of the measurement of the vector was found to be tolerably small, but this does not necessarily mean that the determined vector is actually the true vector for a given individual because: (1) the individual chest contour may differ from the average taken as a basis for the horizontal plane; (2) the individual center may differ from the mean center; (3) the center may shift during the cycle; (4) the anatomic center may not be identical with the electrical center; (5) the electrodes may be misplaced. The effect of these sources of error was investigated, but is not discussed in detail. For items 1, 2 and 4 the probable error was estimated not to exceed 6.5 degrees. Some of the limitations are common to all methods of determination of spatial vectors.

Conclusions and Summary

A simple method to determine spatial vectors of the mean or instantaneous deflections, based on the present electrocardiographic routine procedure, is described. The vectors are given in terms of a horizontal angle (azimuth), a vertical angle and magnitude, and also of the angle between spatial vectors. The time required for the determination of a spatial vector is about three minutes. By means of this method, the spatial vectors are accessible to quantitative analysis and statistical evaluation, instead of qualitative description as in most of the existing literature on spatial vectorcardiography.

The method is based on the determination of the direction of the vector in the horizontal plane from the precordial leads, and of the direction and magnitude in a frontal plane from lead I and III.

The horizontal plane is a circle with lead projections marked on its periphery in terms of angles from a center which was the mean center found from measurements of the chest plates of 72 normal males. The transverse diameter represents lead I and is divided into units corresponding to lead I.

The apparatus consists of the horizontal plane as a base and a metal sphere held by a rectangular metal arm at a height of 21 units (= 10.5 inches) above. The vectors are represented by steel stems on a magnetic base with pole shoes fitting to the metal sphere and with movable ring marks for the end point of the vectors. This point is found as intercept of the direction in the horizontal plane and the height above that plane is determined by means of a special chart.

The probable error of measurement of spatial angles as calculated from the standard deviations of two independent measurements in 30 normal subjects is of the order of ±5 degrees, and that of the magnitude of vectors is about ±1.0 (= 0.1 mv) and ±0.6 mm. for the QRS and T vector.

There is a consistent difference for the horizontal angle when V_1, V_2 and V_3 are taken at the fifth intercostal level and in the conventional location. Therefore, all leads should be taken to the fifth level, and extended sufficiently far to the right or left to include a negative deflection. This is the only modification of present routine electrocardiography which is suggested. Preliminary results illustrate the advantage of this approach in the quantitative characterization of specific abnormalities. The limitations of this method are discussed.

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SUMARIO ESPAÑOL

Los presentes métodos de analisis para vectores espaciales son mas descriptivos que cuantitativos o requieren calculaciones muy largas. Con el analizador de vector espacial, el vector espacial se edifica del electrocardiograma convencional, con solamente leves modificaciones de la rutina electrocardiográfica. El método es simple, puede aplicarse a vectores promedio o vectores instantáneos y una caracterización cuantitativa de cualquier vector en términos de ángulo horizontal o vertical y magnitud puede obtenerse en aproximadamente 3 minutos. Se puede esperar que la descripción de una desviación en términos simples y cuantitativos mejorará la interpretación electrocardiográfica eliminando la deformación resultante de la limitación de un solo plano frontal.

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Effects of Posture on Renal Excretion of Sodium and Chloride in Orthostatic Hypotension

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Large decreases in the rates of sodium excretion, chloride excretion, and glomerular filtration were observed in patients with orthostatic hypotension when they assumed the upright posture following a period of recumbency. When they returned to the recumbent position, sodium excretion typically was not restored immediately in spite of immediate restoration of filtered sodium load. The decreased sodium excretion found to occur in patients with orthostatic hypotension when they are in the upright posture is considered to be due in part to the decreased filtered sodium load and in part to changes in tubular reabsorption that are independent of filtered sodium load.

WHEN the normal human subject changes from the recumbent to the erect position, arterial blood pressure is maintained,[1] and there is either no change or only a moderate decrease in renal sodium excretion.[2-6] When the patient with orthostatic hypotension changes from the recumbent to the upright posture a marked fall in arterial blood pressure occurs[7-18]; therefore, it might be anticipated that the decreased arterial blood pressure in the upright posture would be reflected by a decreased intraglomerular pressure, decreased glomerular filtration rate, and decreased sodium excretion.

The effect of posture upon the renal excretion of sodium in human subjects with orthostatic hypotension has not been reported previously. Studies of renal function in orthostatic hypotension have demonstrated a decreased rate of urine flow when such patients change from the recumbent to the upright position,[13-18] while at the same time, phenolsulfonphthalein excretion[13-15] and uric acid clearance[16] remain unchanged. Corcoran and associates have demonstrated decreased inulin and Diodrast clearances in patients with orthostatic hypotension who were tipped by means of a tilt-table to the 60 degree head-up passive erect posture.[18]

In the present study it has been demonstrated that in orthostatic hypotension large changes in the renal excretion of sodium result from changes in body posture. Filtered sodium loads have been measured, and the changes in sodium excretion have been interpreted in terms of alterations in the glomerular filtration and tubular reabsorption of sodium.

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METHODS

1. Clinical Methods. Studies of renal function were performed upon three patients with orthostatic hypotension and upon one hypertensive patient under the influence of Dibenamine. Changes in renal function were obtained simply by requesting the patient either to assume a position of recumbency or to sit, stand quietly, or walk. In general, a period of erect posture was interposed between two periods of recumbent posture. Arterial blood pressures, pulse rates, fluid intake, and urine output were recorded. Diets were unrestricted except in experiment 6, in which case the patient was fasting, and in experiment 7, in which instance the patient was on a diet containing about 1.5 Gm. of sodium chloride per day. To assure an adequate urine output for urine volume measurements the patients drank varying quantities of water at the beginning of each study and throughout the course of the study. No intravenous infusions were employed. Urine samples were obtained without employment of catheterization. Blood samples were withdrawn from an antecubital vein either at the midpoint of the urine collection period or at the beginning and end of the urine collection period.

The endogenous creatinine clearance was employed as a measure of glomerular filtration rate. Although endogenous creatinine clearance is not always equal to inulin clearance, evidence is accumulating that this function is a reliable measure of changes in glomerular filtration rate.[19-21] In some

experiments urinary creatinine excretion was measured instead of endogenous creatinine clearance.

2. Analytic Methods. Sodium and potassium ions were determined by means of a Barclay Flame Photometer with lithium ion employed as the internal standard.[22] The average deviation of the sodium determinations was about 5 per cent.

Chlorides were determined by the method of Volhard.[23]

Ammonia nitrogen and urea nitrogen in urine samples were determined by an aeration method described by West and Todd.[24]

Creatinine was determined in urine and plasma samples by a modification of the method of Hare.[2] This method allows for determination of "true creatinine" and not "total creatinine chromogen."

TABLE 1.—*Summary of Fluid Intake and Urine Output for All Experiments*

Time	Position	Water Drunk (ml.)	Urine Output (ml.)	Urine Specific Gravity
		Experiment 1		
10:30 p.m. to 7:30 a.m.	Recumbent	Unrestricted	715	1.015
7:30 a.m. to 3:30 p.m.	Upright	Unrestricted	163	1.025
		Experiment 2		
10:00 p.m. to 6:00 a.m.	Recumbent	Unrestricted	1510	1.008
6:00 a.m. to 2:00 p.m.	Upright	Unrestricted	44	1.028
2:00 p.m. to 10:00 p.m.	Upright	Unrestricted	302	1.031
		Experiment 3		
7:15 p.m. to 10:05 p.m.	Standing	800	175	1.010
10:05 p.m. to 11:05 p.m.	Recumbent		385	1.001
11:05 p.m. to 3:05 a.m.	Recumbent		1206	1.003
3:05 a.m. to 7.05 a.m.	Recumbent		285	1.013
7:05 a.m. to 8:05 a.m.	Standing	500	22	
8:05 a.m. to 11:05 a.m.	Standing		25	
11:05 a.m. to 3:17 p.m.	Standing	500	45	1.025
3:17 p.m. to 7:00 p.m.	Standing	800	85	1.027
		Experiment 4		
7:45 p.m. to 6:30 a.m.	Recumbent	Unrestricted	1010	1.015
7:45 a.m. to 4:00 p.m.	Upright	Unrestricted	310	1.035
		Experiment 5		
8:15 a.m. to 12:53 p.m.	Recumbent	500	1860	1.008
12:53 p.m. to 5:14 p.m.	Standing and walking	1000	94	1.021
5:14 p.m. to 6:17 p.m.	Recumbent	250	192	1.007
6:17 p.m. to 8:00 p.m.	Recumbent		940	1.003
		Experiment 6		
2:55 p.m. to 5:50 p.m.	Recumbent	1040	76	1.035
5:50 p.m. to 8.55 p.m.	Sitting	800	167	1.015
8:55 p.m. to 9:50 p.m.	Head-down 27 min.; recumbent 18 min.	500	277	1.005
9:50 p.m. to 12:06 a.m.	Recumbent	450	632	1.003
8:35 a.m. to 11:29 a.m.	Recumbent	400	402	1.002
11:29 a.m. to 2:30 p.m.	Sitting and walking	350	160	1.004
2:30 p.m. to 5:30 p.m.	Recumbent	350	440	1.001

RESULTS

Data concerning fluid intake, urine output and urine specific gravity are listed in table 1

In figures 1 to 7 the postural variations in urinary sodium excretion are shown graphically with the simultaneous variations in either endogenous creatinine clearance* or in urinary creatinine excretion. In those cases in which serum sodium was measured, the filtered

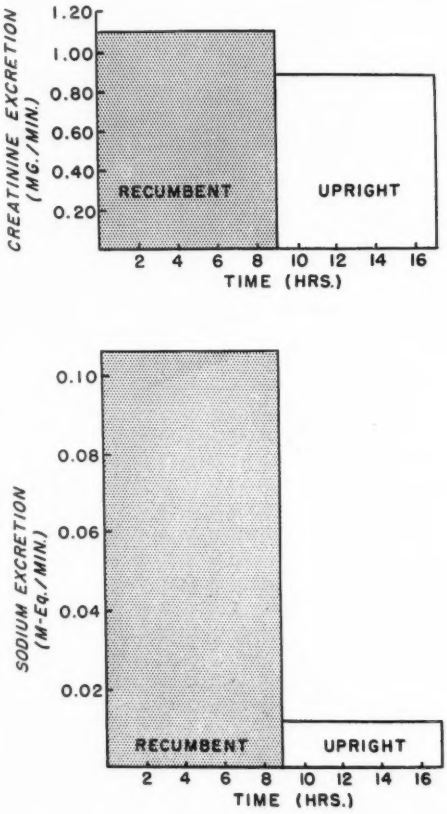

FIG. 1. Effects of posture upon sodium excretion and creatinine excretion in patient, R. N., experiment 1. Patient R. N. was diagnosed as having orthostatic hypotension. From 10:30 p.m., June 8, 1950 to 7:30 a.m., June 9, 1950 the patient was recumbent, asleep most of the time. From 7:30 a.m. to 3:30 p.m., June 9, 1950, the patient was in either the sitting or standing posture.

sodium load, which is equal to the product of the endogenous creatinine clearance and the serum sodium,† is also shown. Protocols of the individual experiments are presented as the legends of figures 1 to 7. In figure 8 the simultaneous excretion rates of potassium, ammonia nitrogen, and urea nitrogen are graphed with the postural changes in the creatinine and sodium excretion rates. The rate of urinary chloride excretion was determined in all cases and found to approximate closely the rate of sodium excretion. An example of this correlation is presented in figure 9.

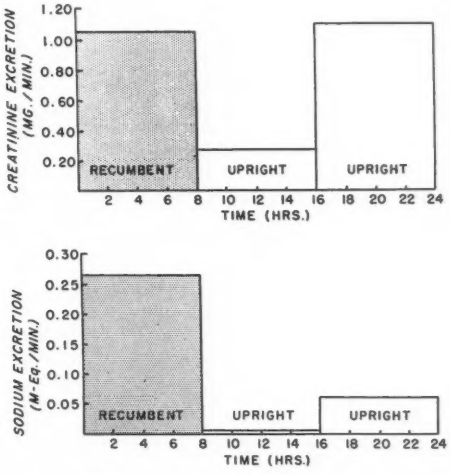

FIG. 2. Effects of posture upon sodium excretion and creatinine excretion in patient, S. B., experiment 2. Patient S. B. had idiopathic orthostatic hypotension. He remained recumbent from 10:00 p.m., Dec. 4, 1950 until 6:00 a.m., Dec. 5, 1950. For the next 16 hours the patient was in either the sitting or standing position, occasionally walking.

The renal excretion of sodium was found to decrease greatly in the patients with orthostatic hypotension when they assumed the upright posture after a period during which they were recumbent. The rate of sodium excretion of the patient in the upright posture was found to be one-third to one-hundredth of the rate in the recumbent posture. A large percentage decrease in sodium excretion while the patient was in the upright posture occurred even in experiment 7, in which the patient was on a "salt-free" diet and excreting only minute quantities of sodium during the control period.

The decreased sodium excretion rate in-

* Endogenous creatinine clearances are uncorrected for body surface area.

† Correction for the Donnan equilibrium and for plasma water content is not applied.

duced by the upright posture was observed to be accompanied by decreases in glomerular filtration rate and filtered sodium load. Relatively small percentage decreases in glomerular filtration rate or filtered sodium load were accompanied by relatively large decreases in sodium excretion rate. In three experiments, 3, 5, and 6, filtered sodium load and urinary

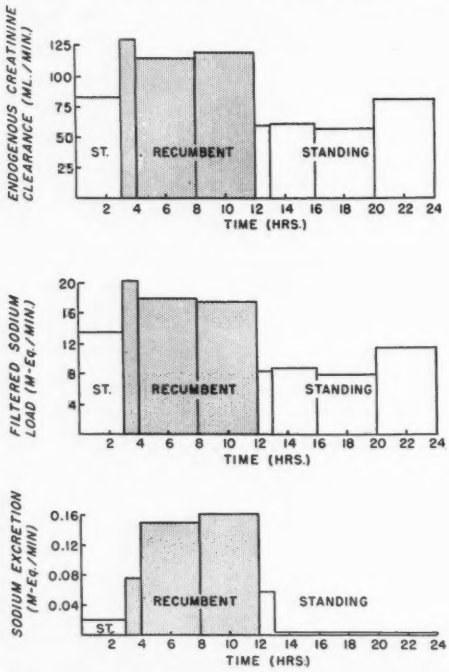

FIG. 3. Effects of posture upon endogenous creatinine clearance, filtered sodium load, and sodium excretion in patient, S. B., experiment 3. The patient, S. B., the same as in experiment 2, was hospitalized from Jan. 23, 1951 to Jan. 24, 1951. Average blood pressure during this experiment when the patient was in the recumbent position was 130/80; pulse, 64; average blood pressure while the patient was standing was 95/80; pulse, 90.

sodium excretion were found to change simultaneously in opposite directions.

In experiment 5 restoration of the glomerular filtration rate and filtered sodium load to the levels obtained while the patient was in the recumbent position occurred without restoration of urinary sodium excretion. In experiment 3, the initial rise in filtered sodium load is accompanied by a delayed increase in sodium excretion. The trend is also seen in experiment 2, in which urinary creatinine excretion returned to the value obtained during the period of recumbency, while urinary sodium excretion remained depressed. On the other hand, in experiment 7, urinary sodium excretion returned to the value obtained while the patient was recumbent in spite of the failure of the filtered sodium load to return to the level observed during recumbency.

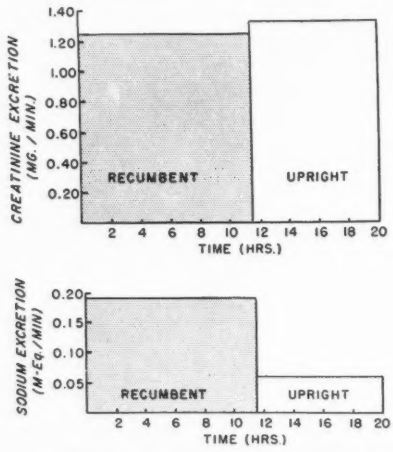

FIG. 4. Effects of posture upon sodium excretion and creatinine excretion in patient, S. B., experiment 4. This study of patient, S. B., was made about one year after experiments 2 and 3. Blood pressure was 110/70 in the recumbent position and 60/40 in the standing position. The patient was not hospitalized but was instructed carefully in the collection of urine samples at home. Diet and fluid intake were unrestricted. The patient remained recumbent from 7:45 p.m., Dec. 15, 1951 to 6:30 a.m., Dec. 16, 1951. He then arose and remained in the upright position, either sitting or standing, from 6:30 a.m. until 4:00 p.m., Dec. 16, 1951.

In experiment 3, figure 3, during *hour 12*, a decrease in sodium excretion is seen to accompany a decrease in the endogenous creatinine clearance. During *hour 13* a further decrease in sodium excretion occurs in the face of an unchanged glomerular filtration rate and filtered sodium load. While it is possible that the urine sample of *hour 12* may have been contaminated with sodium from the urine of *hours 8 to 12*, inspection of figure 8, concerning the same experiment, reveals no corresponding

rend in the excretion of ammonia nitrogen or otassium.

Discussion

In patients with orthostatic hypotension he renal excretion of sodium decreases markdly when the subject assumes the standing osture. The decreased sodium excretion in the atient in the upright posture is accompanied

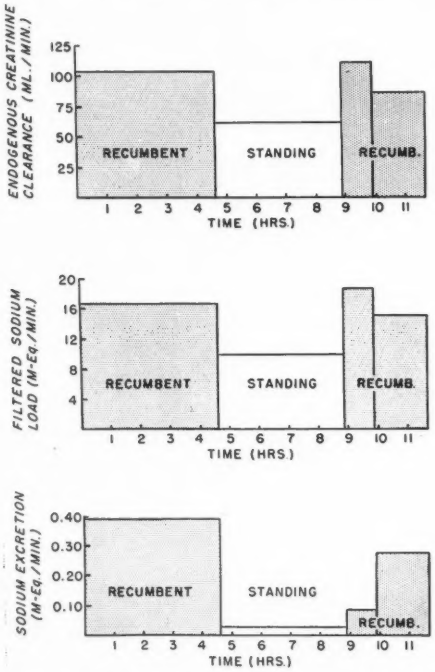

Fig. 5. Effects of posture upon endogenous creatinine clearance, filtered sodium load, and sodium excretion in patient, S. B., experiment 5. Average blood pressure in the recumbent position was 160/90, pulse, 64; and in the standing position, 100/75, pulse, 80.

by large decreases in glomerular filtration rate and filtered sodium load. This is in contrast to the situation in the normal individual who is up and about in whom, at most, relatively minor decreases in sodium excretion[2-6] and glomerular filtration rate[2, 26] occur.

In recent years the relative importance of the glomerular filtration and the tubular reabsorption of sodium upon sodium excretion by the kidney has been the subject of many

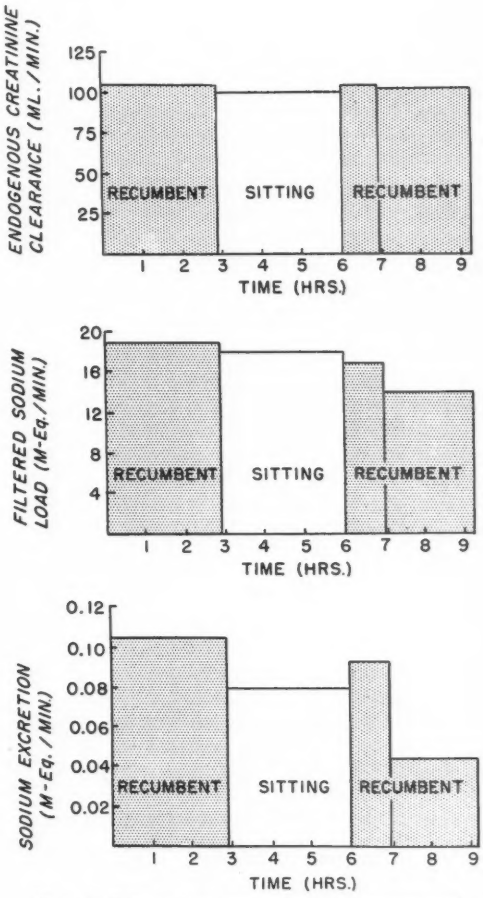

Fig. 6. Effect of posture upon endogenous creatinine clearance, filtered sodium load, and sodium excretion in patient, D. R., experiment 6. D. R., a hypertensive, tuberculous patient, was studied while under the influence of Dibenamine, administered as a diagnostic test for possible pheochromocytoma. No food was allowed for 12 hours prior to the test and for the duration of the urine collection periods. Renal function studies were performed with the patient in the recumbent position and in the partial sitting posture with the head, neck, and trunk elevated 30 degrees to 45 degrees from the horizontal by means of pillows. The foot of the bed was elevated on shock blocks for a brief period (table 1, experiment 7, "Head-down 27 minutes"). The patient's blood pressure averaged 195/125 in the recumbent position; 160/110 in the partial sitting position.

investigations in both man and in experimental animals. Some workers have demonstrated that changes in renal sodium excretion are

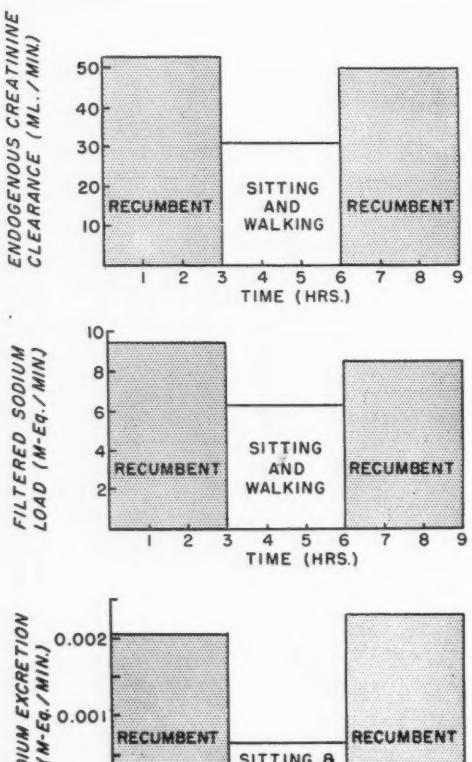

FIG. 7. Effects of posture upon endogenous creatinine clearance, filtered sodium load, and sodium excretion in patient, S. D., experiment 7. S. D. was hospitalized with the diagnoses of pernicious anemia and orthostatic hypotension. In the outpatient department, prior to her hospital admission, her blood pressure in the recumbent position was 110/70 and in the standing position, 60/40. The patient had been on a "salt-free" diet (1.5 Gm. NaCl per day) for at least 10 days prior to the renal function studies and was maintained on the same diet for the duration of the studies. She drank 200 ml. of water at the beginning of the experiment and then 100 ml. of water hourly until its conclusion. During the upright period the patient sat in a wheelchair most of the time. Two periods of ambulation, each of 20 minutes duration, were included in the upright period. Blood pressure while the patient was recumbent averaged 100/70; pulse, 56. Systolic blood pressure, taken while the patient was in the sitting position, was 90 mm. Hg and diastolic pressure could not be determined by the indirect method. Pulse was 72. Hemoglobin, 13.3 Gm.; red cell count, 4.7 million per cubic millimeter.

frequently associated with, and possibly are caused by, somewhat parallel changes in glomerular filtration rate.[27, 28] Others have reported changes in sodium excretion occurring independently of changes in glomerular filtration rate.[29-33]

That alterations in amount of sodium filtered play a role in the decreased sodium

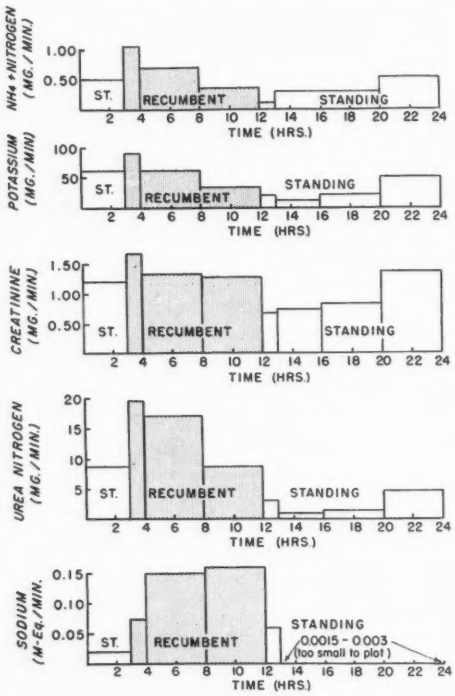

FIG. 8. Effects of posture upon urinary excretion of ammonia nitrogen, potassium, creatinine, urea nitrogen, and sodium, experiment 3. The data depicted here were recorded simultaneously with those shown in figure 3. For further explanations see text.

excretion which occurs in subjects with orthostatic hypotension when they assume the erect posture is indicated by the results of experiment 3 shown in figures 3 and 8. Ammonia nitrogen and potassium, substances excreted by tubular secretion, are little affected by the decrease in glomerular filtration rate occurring during the second period of standing. Creatinine, a substance which is considered to be excreted only by glomerular filtration, under the conditions of the experiment, is decreased

proportionately to the decrease in glomerular filtration rate. In the case of urea, a substance not reabsorbed by an active process, the decrease in urea excretion results from the decreased glomerular filtration rate. Since the percentage decrease in urea excretion is greater than the percentage decrease in creatinine excretion, the decreased glomerular filtration of urea must secondarily result in more complete tubular reabsorption of urea by simple physical processes. Sodium resembles urea insofar as it is also a freely-diffusible substance. By analogy, the decreased filtered sodium load occurring when the subject is in the upright posture may also allow for more complete tubular reabsorption of sodium by simple physical processes. The greater percentage decrease in the excretion of sodium as compared with the percentage decrease in the excretion of urea is evidence that in addition to simple physical processes, an active tubular transport mechanism may be operating to effect reabsorption of sodium.

To prove the occurrence of changes in the active tubular reabsorption of sodium it is necessary to demonstrate different rates of sodium excretion at the same filtered load[34, 35] or to show that sodium excretion and filtered sodium load are changing simultaneously in opposite directions. Many of the investigators claiming to have demonstrated altered tubular reabsorption of sodium have not measured filtered sodium loads. They determined glomerular filtration rates and assumed that the plasma sodium level remained unchanged. In the present work serum sodium levels have been determined and the filtered sodium loads calculated. Evidence has been obtained that sodium excretion may vary independently of filtered sodium load. In experiment 3, figure 3, during the recumbent period, sodium excretion is seen to increase while filtered sodium load is decreasing. During the early part of the second period of standing, a marked decrease in sodium excretion occurs in the face of an unchanged filtered sodium load. During the last period of standing, sodium load tends to be restored towards control values without an accompanying increase in sodium excretion. In experiment 6, during *hour 6*, sodium excretion increased in spite of a decreasing filtered sodium load. In experiment 7, figure 7, filtered sodium load remains below the level observed during the last recumbent period, while sodium excretion returns to above the control level.

The results indicate that changes in sodium excretion which are due to altered filtered sodium load occur rapidly, whereas the adjustments in tubular reabsorption occurring independently of changes in filtered sodium load occur more slowly. During the recumbent period in experiment 3, figure 3, an immediate rise in filtered sodium load is accompanied by a gradual increase in sodium excretion. In the same experiment a sudden decrease in filtered sodium load is accompanied by a simultaneous decrease in sodium excretion; however, a further decrease in sodium excretion occurs with the passage of time, in spite of no further change in filtered sodium load. In experiment 5, figure 5, an immediate restoration of filtered

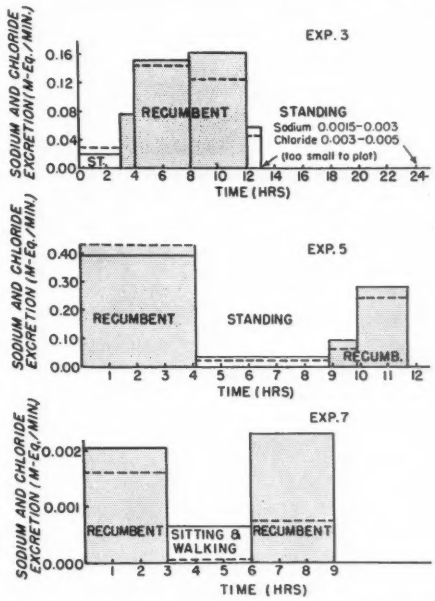

FIG. 9. Comparison of the changes in urinary sodium excretion and chloride excretion resulting from changes of posture in experiments 3, 5, and 7. The sodium excretion is indicated by the solid horizontal lines, while the chloride excretion is indicated by the broken horizontal lines. When the two were equal, a single solid horizontal line is employed.

sodium load to the previous value for the recumbent posture is seen to be accompanied by a more gradual rise in sodium excretion rate.

From these studies it appears that a sudden large decrease in glomerular filtration rate and filtered sodium load may cause a sudden severe decrease in sodium excretion. Later adjustments in tubular reabsorption, occurring independently of glomerular filtration rate and filtered sodium load, may tend to alter sodium excretion further, depending upon variables not yet clearly identified.

Summary

The changes in renal sodium excretion resulting from changes of posture in patients with orthostatic hypotension have been measured and the results interpreted in terms of alterations in the glomerular filtration and the tubular reabsorption of sodium. The endogenous creatinine clearance was employed as a measure of the glomerular filtration rate, and filtered sodium loads were calculated as the products of the glomerular filtration rates and the serum sodium concentrations.

Large decreases in the rate of urinary sodium excretion and in glomerular filtration rate occurred when subjects with orthostatic hypotension changed from the recumbent to the upright posture. Typically, when they returned to the recumbent posture sodium excretion was not restored immediately in spite of the immediate increases in filtered sodium loads. Other examples of sodium excretion varying independently of filtered sodium load were observed; thus proof was obtained of altered tubular reabsorption of sodium. Changes in chloride excretion resulting from postural changes in patients with orthostatic hypotension were parallel and approximately equal to the changes in sodium excretion.

It is concluded that the decreased sodium excretion found to occur in patients with orthostatic hypotension when they were in the upright position is partly due to the decreased load of sodium filtered and partly due to changes in tubular reabsorption that are independent of filtered sodium load.

Sumario Español

Gran diminución en la velocidad de excreción del sodio y cloruro, y la filtración glomerular fueron observados en pacientes con hipotensión ortostática al asumir la posición vertical luego de un período de reclinación. Cuando volvieron a la posición reclinada, la excreción de sodio típicamente no fue restaurada inmediatamente a pesar de inmediata restauración de la carga de sodio filtrado. La diminución de excreción de sodio encontrada en pacientes con hipotensión ortostática cuando en la posición vertical es considerada como causada en parte a la diminución de carga de sodio filtrado y en parte a cambios en la reabsorción tubular que son independientes a la carga de sodio filtrado.

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Acute Effects of Elevation of Coronary Sinus Pressure

By Richard W. Eckstein, M.D., J. Carl Hornberger, M.D., and Toyomi Sano, M.D.

The acute physiologic effects of the aorta to coronary sinus anastomosis of Beck have been studied. The evidence presented shows that arterialization of the coronary sinus results in a small retrograde flow from the sinus through capillaries into the occluded artery and that such retrograde flow supplies from 14 to 25 per cent of the normal myocardial oxygen requirement. It is suggested that this is insufficient to maintain normal myocardial contraction, but probably prevents ventricular fibrillation. However, when the sinus is arterialized in the presence of normal or reduced coronary flow electrocardiographic and coronary inflow data show that there is myocardial anoxia. This is probably due to the restriction in capillary outflow and results in an expansion of the coronary vascular bed.

THIS IS A continuation of previous studies[1, 2] undertaken to investigate the acute and chronic effects of the operation developed by Beck and his associates[3-7] to produce an anastomosis between the aorta and the coronary sinus with subsequent partial sinus ligation. The aim of the procedure is to revascularize the human heart in occlusive coronary artery disease. An examination of the evidence presented by our own acute experiments along with that concerning the chronic dogs of Beck[7] leaves no doubt that elevation of coronary sinus pressure favorably modifies the generally fatal effects of the acute occlusion of a major coronary artery in the dog. Gross,[8] Robertson[9] and Ungerleider[10] had previously shown that partial or complete sinus ligation or sinus pressure elevation resulted in a reduction in the size and number of infarcts and in the mortality following coronary artery occlusion. Roberts[11] was able to maintain dogs for 26 hours after coronary occlusion by connecting an artery to the coronary sinus with a glass cannula. The work of others has been less optimistic.

Gregg and his associates[12, 13, 14] studied this problem in detail and showed that elevation of sinus pressure augmented peripheral coronary pressure and retrograde flow, which changed from the normal arterial blood to venous blood containing only about 3 volumes per 100 cc. of oxygen. They were unable to demonstrate that sinus pressure elevation preserved myocardial contraction distal to a ligated artery even when arterial blood was forced into the sinus, and therefore, concluded that the acute procedure failed to benefit the coronary circulation. Likewise Shipley[15] in acute experiments with the coronary sinus perfused by an artery was unable to demonstrate aid to the cardiodynamics following blockage of left coronary inflow.

Notwithstanding these pessimistic findings the reinvestigation of this problem is justified by the observations[1, 2] that sinus pressure elevation serves to prevent the usual ventricular fibrillation following acute coronary occlusion. The explanation of acute benefit derived from sinus pressure elevation following coronary artery occlusion on the basis of improved myocardial oxygenation due to retrograde capillary flow requires certain evidence. First, it necessitates the demonstration that the anatomic connections between capillaries and veins actually allow retrograde flow. Such reversed flow may be impossible due to the effective action of venous valves or to

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Dr. Hornberger is participating in this work during the tenure of a Heart Traineeship of the National Heart Institute, U. S. Public Health Service. Dr. Sano is a Fellow from the University of Tokyo, Japan.

peculiarities in the anatomic arrangement of capillaries and veins which results in blockage with venous pressure elevation. Second, there must be channels to serve as adequate drainage from the occluded artery. The observations of Wearn[16] show that such an artery is not a dead end system, but does have potential drainage channels in the form of arterioluminal and arteriosinusoidal vessels. Evidence that these channels are functional is lacking. In addition there are large posterior veins opening into the ostium of the sinus or right auricle which do not share in sinus pressure elevation. Retrograde blood into the circumflex artery might escape into these veins through a second set of capillaries. Likewise the anterior cardiac veins may serve to drain the anterior descendens artery in a similar manner.[17, 18, 19] Third, a suitable pressure differential between the coronary sinus and the artery must be present. Such is not the case in the normal dog whose coronary arteries are supplied from the aorta. However, after coronary artery occlusion an effective pressure differential is possible prior to the development of collateral vessels provided there is an escape route from the artery and the sinus pressure can be maintained at suitable levels. Fourth, in order for retrograde flow to benefit the myocardium it must be shown that such blood flows in sufficient quantities and gives up its oxygen during its capillary passage. That reversed flow of blood is accompanied by oxygen exchange has been shown by Heimbecker[20] in the case of the gut, but has not been demonstrated in the heart.

In an effort to answer these and other questions these studies have been concerned with the influence of the elevation of coronary sinus pressure on normal coronary inflow, amount and nature of backflow, peripheral coronary pressure, electrocardiograms, coronary sinus pressure, cardiac output and in the microscopic appearance of the myocardium and coronary vessels. Due to the magnitude of the data and the fact that the findings in the acute experiments differ widely from the findings in the chronic dogs prepared by Beck, the observations are being reported separately. This then is a study limited to the acute effects of elevation of coronary sinus pressure.

Methods

Mongrel dogs were anesthetized with morphine and pentobarbital. Respiration was maintained by intermittent positive pressure applied through a tight fitting rubber tube placed within the trachea. The left jugular vein was exposed and a glass cannula passed to the level of the right auricle. This served to administer intravenous fluids and to return coronary sinus blood to the animal. A long metal cannula was passed through the right common carotid artery to the aorta for optical registration of aortic blood pressure and in some cases to perfuse either the descendens or the circumflex coronary artery. The left chest was entered between the fourth and fifth ribs which were widely spread. A ligature was passed about the coronary sinus near its origin and was tied about the tip of a cannula introduced through the tip of the right auricle. This cannula had either a double lumen as previously described,[1] or had only a single lumen with a side arm for connection to the cannulated subclavian artery. In some instances an attempt was made to partially isolate the major venous drainage of the anterior descendens and circumflex arteries. In these cases a plastic tube was passed through the single lumen coronary sinus cannula. This tube was fixed in the great cardiac vein by means of a ligature. The blood from the great cardiac vein was led into the left jugular cannula. Arrangements were made so that pressure could be raised in either or both the great vein and the coronary sinus by clamping and/or perfusion from the subclavian artery. Usually the circumflex artery was cannulated and perfused through a Shipley recording rotameter[21] to indicate the amount as well as the changes in inflow. In a few experiments the anterior descendens artery or the total left coronary artery was used. In the latter instance the special coronary cannula[22] was employed. In certain experiments to study the mechanisms of coronary inflow changes, the constant perfusion pressure chamber[23] was used. Optical recordings were made of coronary perfusion pressures, and coronary sinus pressure. The animals were given 150 to 200 mg. of heparin to prevent fibrin formation in the rotameter. Electrocardiograms were recorded usually from lead aV_R.

Arrangements were made for measurements of peripheral coronary pressures distal to the point of clamping as well as the amounts of backflows at atmospheric pressure. In many instances the oxygen content of the back flowing blood was determined by the method of Neill and Van Slyke.[24]

Finally, a series of experiments were performed to study changes in left ventricular output. The thoracic aorta was cut and the blood diverted through a large Shipley[21] recording rotameter with the brachiocephalic and subclavian arteries supplied from the outflow side as described previously.[25]

Results

A. Effects of Sinus Pressure Elevation on the Source, Amount and Nature of Backflow

Figure 1 shows the salient anatomic arrangement of the coronary circulation. It also indicates the ligated circumflex artery which has been cannulated peripheral to the ligature. When the coronary cannula is open to atmospheric pressure, it has been shown that from 0.5 to 5.8 cc. of arterial blood flow from the peripheral artery.[26] This backflow largely

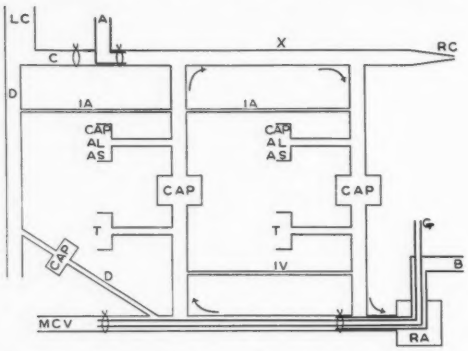

FIG. 1. Diagram of circumflex artery and coronary sinus. *A*, cannula in circumflex artery; *B*, cannula tied in ostium of coronary sinus; *C*, circumflex artery; *D*, anterior descendens artery; *L. C.*, common left coronary artery; *I. A.*, interarterial collaterals; *C. A. P.*, capillary bed; *A. L.*, arterioluminal vessels; *A. S.*, arteriosinusoidal vessels; *D*, vein; *T*, thebesian vein; *I. V.*, intervenous anastomosis; *G*, plastic cannula ligated in great cardiac vein (*MCV*); *R. A.*, right auricle; *R. C.*, right coronary artery; *X* point of second circumflex cannulation; arrows indicate direction of flow with sinus pressure elevated when back bleeding from *A* is prevented. (See text.)

originates in nonoccluded coronary arteries and reaches the cannulated artery through small normally present interarterial collaterals. In these present experiments the backflows from the circumflex artery ranged from 0.8 to 7.6 cc. with an average of 2.8 cc. When sinus pressure is elevated by partial or complete occlusion or by the connection of the sinus to a systemic artery the backflow increases and becomes venous in character. Table 1*A* shows that as the pressure in the arterialized sinus is increased from a mean pressure of 30 mm. Hg to 90 mm. Hg the backflow increases from 6 to 11.6 cc. per minute and the oxygen content decreases.

Although this is substantial evidence that elevation of sinus pressure produces a true reversed capillary flow which originates in the sinus, Gregg[13] noted that the increased backflow following sinus occlusion could largely be abolished from the descendens simply by clamping the circumflex artery. However, he makes no reference to possible changes in sinus pressure.) It was found in these experiments that sinus pressure previously elevated by complete sinus occlusion dropped considerably when the second major branch of the left coronary artery was clamped. This is understandable, since clamping of the total left coronary largely removes the last remaining source of sinus blood. However, no drop in sinus pressure occurs when the sinus is perfused by a systemic artery. Table 1*B* shows the results of such an experiment. Clamping of the anterior descendens artery in the presence of the arterialized sinus results in a decrease in backflow from 12.4 to 8.8 cc. per minute due to removal of the normal interarterial backflow. This results in no change in sinus pressure. However, clamping of anterior descendens artery in the presence of sinus occlusion without arterialization, reduces the backflow from 11.6 to 3.2 cc. per minute and is accompanied by a considerable reduction in sinus pressure. These and the results of similar experiments (see table 2*B*, experiment 115) support the conclusion that the coronary sinus is the immediate source of the increase in backflow which occurs when coronary sinus pressure is elevated.

The final two observations in table 1*C* show averages of eight experiments with the coronary sinus occluded to produce a mean sinus pressure of 50 mm. Hg and averages of eight experiments in which the coronary sinus was arterialized to produce a mean sinus pressure of 50 mm. Hg. Although both groups had equal mean sinus pressures, the backflow in the arterialized group is substantially higher. Examination of the optically recorded actual sinus pressures provides the reason since arterialization of the sinus results in a sinus diastolic pressure of 28 mm. of mercury as compared with 16 mm. of mercury found in the

TABLE 1.—*Pressure Relationships Affecting Retrograde Flow*

Exper. No.	Condition of		Pressures mm. Hg			Backflow at Occluded Circumflex Artery cc./min.	Oxygen from Occluded Circumflex Artery Vol. %
	Sinus	Anterior Descending Artery	Aorta	Circumflex Artery	Coronary Sinus		
	A. Effect of Arterialization at Various Pressures						
R-111	Arterialized at 30 mm. Hg	Normal	112/86	30/?	40/23	6.0	6.2
	Arterialized at 60 mm. Hg	Normal	100/80	38/?	70/36	9.6	4.0
	Arterialized at 85–90 mm. Hg	Normal	99/79	46/22	100/52	11.6	3.3
	B. Effect on Anterior Descendens Artery with Arterialized and Occluded Sinus						
R-113	Arterialized at 50 mm. Hg	Normal	122/90	50/18	68/40	12.4	
	Arterialized at 50 mm. Hg	Occluded	130/82	45/15	70/43	8.8	
	Occluded at 50 mm. Hg	Normal	122/88	40/14	83/14	11.6	
	Occluded at 50 mm. Hg	Occluded	133/98	30/8	50/22	3.2	
	Normal	Normal	112/72	25/10	12/3	6.0	
	C. Comparison of Arterialized and Occluded Sinus						
	Occluded (Ave. of 8)	Normal	125/97	35/13	72/16	5.9	
	Arterialized (Ave. of 8)	Normal	119/84	47/17	68/28	9.2	

TABLE 2.—*Studies of the Source of Retrograde Flow*

Exper. No.	Conditions of			Pressures mm. Hg				Backflow at Occluded Circumflex Artery cc./min.	Oxygen Vol. %	
	Coronary Sinus	Great Cardiac Vein	Anterior Descending Artery	Aorta	Circumflex Artery	Great Cardiac Vein	Coronary Sinus		From Occluded Circumflex Artery	Coronary Sinus
	A. Effects of Arterialization of Sinus and/or Great Cardiac Vein									
R-115	Normal	Normal	Normal	93/66	37/15	21/0	Normal	7.6		
	Normal	Arterialized	Normal	92/60	35/13	72/45	Normal	8.0		
	Arterialized	Normal	Normal	90/58	46/18	Normal	73/46	14.00		
	Arterialized	Arterialized	Normal	95/62	46/19	71/43	71/43	16.0		
	B. Effects of Arterialization of Sinus and Great Vein and Decendens Occlusion									
R-115	Normal	Normal	Normal	80/56	32/14	18/0	18/0	7.2		
	Arterialized	Arterialized	Normal	69/44	45/20	70/44	70/44	18.8		
	Arterialized	Arterialized	Occluded	67/49	37/18	70/53	70/53	9.0		
	C. Retrograde Circulation Time with Amount and Oxygen Content of Retrograde Flow									
R-120	Normal	Normal	Normal					1.2		
	Arterialized	Normal	Normal	Peripheral circumflex bleeding to air. P^{32} injected into coronary sinus appeared in retrograde blood in 13 sec.				6.8	3.8	14.7
	D. Retrograde Flow and Oxygen Content from Anterior Descendens Artery									
								Ant. descend.	Ant. descend.	Great vein
R-126	Normal	Normal		Peripheral anterior descendens				0.8		
	Normal	Arterialized		Bleeding to air				10	2.3	8.4

sinus occlusion group. (See also fig. 2 *B* and *C*.) Since cardiac diastole provides optimum conditions for intramural flow the interpretation of these results becomes obvious.

Although no mention has been made of the changes in peripheral circumflex pressure it can be stated in general, as shown in table 1 and figure 2 that these pressures follow the direction of the changes in backflows and sinus pressures under the conditions of these experiments, namely, following brief periods of circumflex occlusion and sinus pressure elevation. Peripheral coronary pressure is always elevated by elevation of sinus pressure and in these acute experiments is always less than coronary sinus pressures. However, in the case of the normal sinus, the peripheral coronary pressure exceeds the sinus pressure.

B. Results of Attempts to Isolate Venous Drainage of the Circumflex Artery

In these experiments the great cardiac vein was drained separately through the long plastic cannula as shown in figure 1. The drainage from the circumflex artery in some instances was reasonably well isolated from that from the anterior descendens artery. Such a situation served two purposes: (1) It permitted more definite information as to the source of coronary backflow with coronary venous pressure elevation. (2) It provided conclusive evidence as to the pathways concerned in the retrograde flow.

Table 2 shows the results of typical experiments. In *A* it can be seen that arterialization of the great cardiac vein raised the backflow from 7.6 to but 8.0 cc. per minute, that arterialization of the coronary sinus augmented the backflow to 14.0 cc. per minute while arterialization of both sinus and great vein resulted in an addition of only 2 cc. per minute to the backflow. Table 2*B* shows that elevation of pressure in both the great cardiac vein and the coronary sinus increased the backflow from 7.2 to 18.8 cc. per minute, and clamping of the anterior descendens artery reduced the backflow to 9 cc. per minute, which is expected since anterior descendens clamping removes about 7.2 cc. per minute, which is the normal interarterial collateral flow. These experiments are further evidence that the source of the increased backflow is the venous system which drains the artery in question.

In table 2*C* nearly complete isolation of the circumflex artery and its venous drainage was attained since clamping of the circumflex artery reduced the flow from the sinus cannula to only 3.6 cc. per minute. In this experiment blood containing P^{32} and 14.7 volumes of oxygen per 100 cc. of blood which was introduced into the sinus was identified with a Geiger counter and recovered from the circumflex artery within 13 seconds. The fact that the blood was reduced to contain but 3.2 volumes of oxygen per 100 cc. is proof of its capillary passage and provides equally substantial evidence that blood flowing in a retrograde fashion through myocardial capillaries does give up its oxygen. The final experiment in table 2*D* provides similar evidence in the case of the anterior descendens artery.

C. The Question of Retrograde Flow When Backflow to Atmospheric Pressure Is Prevented

The fact that sinus pressure elevation produces reversed capillary flow with the peripheral artery bleeding does not prove that such retrograde flow will occur when the artery is clamped and not allowed to bleed. Although it has been pointed out that drainage channels from the occluded artery are present their functional capacity must be shown. There are three reasons for believing that true reversed capillary flow occurs when backflow is prevented.

1. When the circumflex artery and its venous system are isolated as above, the artery and accompanying vein retain their original color relations as long as the peripheral arterial pressure exceeds the arterialized venous pressure. At roughly identical pressures the artery remains red and the vein becomes red. When the arterial perfusion pressure is further reduced to lower peripheral artery pressure the artery changes color and appears like a vein. Such a situation exists also when the artery is completely clamped from its perfusion source. The same color relationship holds when backflows are being measured. In other words,

he veins serve as arteries, and the arteries as veins.

2. Studies of peripheral pressures show that elevation of sinus pressure produces increases of peripheral coronary pressure which acutely never attain the systolic or diastolic pressure levels of the sinus. (See tables 1 and 2.) If the artery were a dead end system, both the sinus and peripheral coronary pressures should be equal. In order to test whether the elevation in peripheral coronary pressure resulting from sinus pressure elevation is due merely to a blocking of the escape of the normal interarterial flow the following experiment was done. Normal interarterial backflow was measured. The sinus pressure was elevated and blood withdrawn from the peripheral artery in amounts which exceeded the normal interarterial backflow. Although this reduced peripheral coronary artery pressure (P.C.P.) somewhat it remained above the normal level. It is felt, therefore, that the major increase in peripheral coronary artery pressure is due to true retrograde flow.

TABLE 3.—*Amounts of Retrograde Flow into Occluded Artery*

Exper. No.	Normal Backflow	Backflow with Sinus Arterialization cc./min.	Total Backflow Minus Normal Backflow cc./min.	Coronary Sinus Pressure mm. Hg	Circumflex Artery Pressure mm. Hg	Retrograde Flow into Ligated Vessel			
						Calculation Method	Arterial Inflow Method	Sinus Flow Method	Backflow Minus Sinus Inflow Method
A. Measurements and Calculations for Circumflex Artery									
111 to 119	3.4	8.1	4.7	50	37/15				
120 to 125	2.2	6.7	4.5	50	21	2.6			
120	1.2	6.8	5.6	50	20	3.4	6.2	6.3	
121	0.8	5.6	4.8	45	21	2.6	3.7	3.2	4.0
122	5.0	7.2	2.2	50	15	1.5			
124	1.6	3.6	2.0	50	15	1.4	4.0	5.6	1.6
125	2.8	10.4	7.6	50	35	2.3	2.3	3.4	6.6
B. Same for Anterior Descendens Artery									
126	0.8	10.0	9.2	50	28	4.1	6.8	8.0	4.2
128	3.6	6.6	3.0	50	24	1.5			

D. Quantitative Estimation of Retrograde Flow into the Occluded Artery

Although the above observations and a prior reasoning indicate that retrograde flow does occur into the occluded artery, direct measurements of the actual retrograde flow is thus far impossible. However, certain estimations have been made by four different methods.

1. The first method is based upon calculated flows due to pressure differences between the sinus and the peripheral coronary artery. These calculations are expressed by the formula

$$R.F. = B.F. \times \frac{S.P. - P.C.P.}{S.P.}$$

where $R.F.$ = retrograde flow into the occluded artery.

$B.F.$ = total backflow minus normal interarterial backflow from the open peripheral artery.

$S.P.$ = mean sinus pressure.

$P.C.P.$ = mean peripheral coronary pressure with elevation of sinus pressures.

These values are listed in table 3 under the column "Calculation Method".

2. The second method is based on the premise that at equal mean sinus and arterial pressure there is no capillary flow between the veins and artery. The values were obtained in this way. The mean coronary sinus pressure was elevated (usually to 50 mm. Hg) and the resulting peripheral coronary pressure was measured. Then both the sinus and coronary

artery were perfused at the previously measured peripheral coronary pressure. The amount of blood flowing into the artery under these circumstances was measured. The normal interarterial backflow was subtracted from the metered arterial inflow. The results are shown in table 3 (Arterial Inflow Method).

3. This is a reverse of method 2. A rotameter was placed between the subclavian artery and the coronary sinus so as to meter sinus inflow in the venous isolation preparation. The circumflex artery was perfused from the aorta. Mean sinus and peripheral circumflex pressures were set at identical levels of 50 mm. Hg. Sinus inflow was noted. The artery was clamped and mean sinus pressure was maintained at 50 mm. Hg. The increase in sinus inflow was measured and listed in table 3 (Sinus Flow Method).

4. It was noted in the venous isolation preparations that with the sinus pressure elevated and sinus inflow being measured with the peripheral artery bleeding, sinus inflow always decreased when the peripheral coronary artery was closed, that is, when backbleeding was prevented. It, therefore, appeared reasonable that if the decrease in sinus inflow were subtracted from the backflow contributed by the sinus (that is, total backflow minus normal interarterial backflow) the result should be true retrograde flow. These results are listed in table 3 (Backflow Minus Sinus Inflow).

A study of these calculated and measured flows reveal that there is wide variation and even some impossibilities since in experiments R 120 and R 124 some values exceed the amount contributed by the sinus even when operating against atmospheric pressure. However, the accurate measurement of such low flows with a rotameter is difficult. Of more importance, however, is the fact that by all methods there is evidence of retrograde flow into an occluded vessel. Since these flows can never exceed the amounts shown in the fourth column, table 3, the conclusion that their magnitude is indeed small is inevitable.

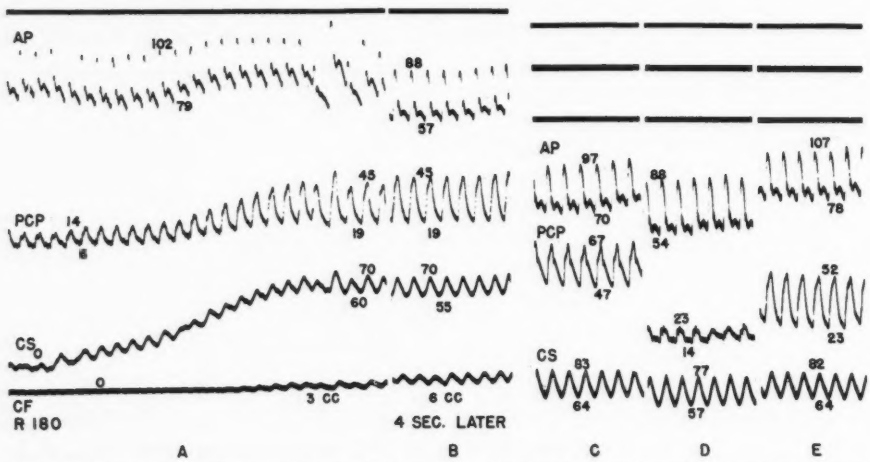

FIG. 2. Shows flow from central circumflex branch to distal circumflex branch induced by arterialization of the coronary sinus in *A* and *B*, as well as changes in total peripheral circumflex pressure. Peripheral pressures in the central branch are shown in *C*, in the distal branches in *D*, and total pressure during flow measurement in *E*. *AP*, Aortic Pressure: *PCP*, peripheral circumflex pressure; *CS*, Coronary sinus pressure; *CF*, flow from central to distal circumflex.

E. Drainage Pathways from Occluded Arteries

Although the previous studies indicate a small retrograde capillary flow based on indirect measurements, certain direct metered values have been obtained. The role of the large posterior veins emptying directly into the right auricle and not sharing in elevation of venous pressure have been investigated. A

second cannula was placed in the circumflex artery and directed peripherally at *X* in figure 1. In some cases a rotameter was connected between the two cannulas. In other cases a calibrated inverted glass U tube was used. The ascending limb of this tube was filled with saline to give a sharp blood-saline junction. Clamping of the artery between the two cannulas usually resulted in no flow in either direction in the presence of normal sinus pressure. However, elevation of sinus pressure gives a prompt flow of from 1.6 to 7 cc. per minute of highly unsaturated blood passing from the central to the peripheral circumflex artery. Flow is first detected at sinus pressures of approximately 30 mm. Hg and steadily increases with the creation of higher sinus pressures. Measurement of the pressures in the central and distal branches reveals adequate pressure differences to explain the direction of flow. For example, in experiment R 181 (not shown) a mean sinus pressure of 60 mm. Hg produced a forward circumflex flow of 1.6 cc. per minute with a total peripheral circumflex pressure of 30 mm. Hg. Mean central circumflex pressure was 38 mm of mercury in contrast to 24 mm. of mercury found in the distal segment. In the same experiment the normal backflow from the central segment was only 0.6 cc. per minute which increased to 3.6 cc. per minute at a sinus pressure of 60 mm. Hg. Backflows from the distal segment were 1.2 and 3.8 cc., respectively. Subtraction of the normal backflow of 0.6 cc. from the metered forward flow of 1.6 cc. leaves a retrograde flow of at least 1 cc. arising from the central circumflex artery. This is indeed small when compared with the normal inflow of 9 cc. per minute in this branch. However, the fact that the central circumflex pressure was but 38 mm. Hg in the face of a sinus pressure of 60 probably indicates other small routes of exit in addition to the distal circumflex artery. That such extra drainage was also venous is likely since venous anastomoses were visible at the apex. Furthermore, at the conclusion of this experiment fluid injected into the central branch of the circumflex flowed both from sinus and posterior veins. In experiment R 180, figure 2, in which the central circumflex branch was very large there was a normal backflow of 1.4 cc. per minute from the central branch which increased to 12.4 cc. per minute with the sinus pressurized at 70 mm. Hg. The flow from central to distal circumflex was approximately 6 cc. per minute while the total circumflex pressure was 35 mm. Hg. When this flow was prevented the pressure in the central branch reached 60 mm. Hg which again probably indicates small additional escape routes.

These experiments are of interest from two standpoints. In the first place the metered flows check closely with the calculated retrograde flows based on differences between the sinus and peripheral coronary pressures. Of more interest, however, are the measurements of the amount and direction of retrograde flows which indicate the importance of the nonpressurized veins.

A consideration of the myocardial area supplied by the entire left coronary serves to demonstrate the magnitude of these accessory veins. It has been clearly shown by Gregg[17] that they are sufficient to drain the left coronary flow which does not appear in the sinus. It has been observed in these experiments that normal left coronary inflow can by no means be abolished even though coronary sinus pressure exceeds coronary perfusion pressure. Such a situation requires a considerable drainage system in addition to the sinus. That the large posterior nonpressurized veins serves in that capacity was shown by its direct cannulation. For example, in experiment R 179 (not shown) there was a flow from the cannulated posterior vein of 8 cc. per minute which decreased to 5.2 cc. per minute when the circumflex artery was occluded. Elevation of sinus pressure augmented the flow to 15.2 cc. per minute. Release of the circumflex artery resulted in a venous outflow of 16.4 cc. per minute. However, even though the peripheral circumflex was allowed to bleed, thereby removing all retrograde and collateral flow, sinus pressure elevation resulted in a flow of 14.8 cc. per minute from the vein. This experiment demonstrates not only the importance of this vein for circumflex drainage, but also shows that a considerable amount of blood introduced into the sinus may escape without passing through capillaries.

Measurement of sinus inflow therefore cannot critically demonstrate retrograde capillary flow.

Finally, when dilute India ink was injected into the sinus it was found that the injected area comprised but from 62 to 82 per cent of the area supplied by the left coronary. The noninjected area included the anterior left border of the right ventricle, an area along the posterior veins and the entire interventricular septum. It is, therefore, believed that these areas contain sizeable accessory veins or

TABLE 4.—*Effect of Continuous Arterialization of Sinus on Peripheral Circumflex Pressure and Retrograde Flow*

Circumflex artery perfused from aorta between measurements. (R-176)

Time after Arterialization of Sinus	Condition of Sinus	Aortic Pressure mm. Hg	Peripheral Coronary Pressure mm./Hg	Sinus Pressure mm./Hg	Backflow cc./min.
min.					
0	Normal	134/115	27/12	2	6.8
2	Arterialized	120/101	40/23	68/42	10.4
30	Arterialized	118/94	38/20	67/40	10
60	Arterialized	100/77	41/27	67/40	10.4
60	Normal	111/90	35/20	1	7.2
90	Arterialized	89/64	41/22	67/35	9.6
120	Arterialized	88/60	44/20	70/30	10
120	Normal	88/65	30/14	1	5.6
150	Arterialized	102/71	51/22	74/27	8
180	Arterialized	89/64	44/18	74/25	6.8
180	Normal	85/61	30/14	1	3.6
195	Arterialized	98/68	47/22	78/34	4.8

possibly thebesian veins in the case of the septum.

F. Studies upon the Degree of Persistence of Backflow

These experiments were done as before except that when the preparation had been completed the sinus was arterialized and at 15 minute intervals the peripheral pressure and the backflow were measured. As shown in table 4, experiment 176, the favorable pressure gradient between coronary veins and peripheral artery, even when allowed to operate over considerable time, failed to induce vascular expansion with increased retrograde flow. Instead the backflows decreased and the peripheral coronary pressure increased slightly to reduce the effective pressure gradient. During these experiments the areas of the heart drained by the pressurized veins became firm to the touch and filled with gross hemorrhage. Similar results were obtained when the artery was permanently clamped or when perfused from the aorta. Evidences of hemorrhage appeared early while the right ventricle and interventricular septum remained normal. Hemorrhage was first seen as small areas in the perivascular fat which enlarged and multiplied to include the entire area. Microscopic examination showed the hemorrhage to be extravascular and to be more pronounced in the subepicardial regions. Also, valves were regularly found even in small veins. It is suggested that the flow and pressure changes are the result of extravascular compression from hemorrhage and possibly edema which not only limits the vascular bed concerned with backflow, but also, with arterial drainage. There is a possibility that the hemorrhage has its origin in the rupture of the attachment of the venous valves.

G. The Effect of Sinus Pressure Elevation on Left Ventricular Output

These studies were done by methods previously described and can be divided into two groups. In the first group sinus pressure was elevated by partial or complete sinus occlusion so as to escape the effects of an arteriovenous fistula. Figure 3*A* and *B*, shows a typical experiment. There is a slow but definite decrease in left ventricular output of 180 cc. per minute. This exceeds the reduction in total venous return due to sinus occlusion. Figure 3*C* shows that sinus arterialization in the presence of complete sinus occlusion likewise results in a decreased output. Eight observations in four experiments reveal an average reduction in output of 207 cc. per minute. It is believed this observed fall in output is of cardiac origin.

In the second group the sinus was open or partially occluded and was arterialized so as to produce an arteriovenous fistula. As indicated in figure 3*D*, the sudden elevation of sinus pressure results in a prompt rise in ventricular output from 920 to 1150 cc. per minute. In

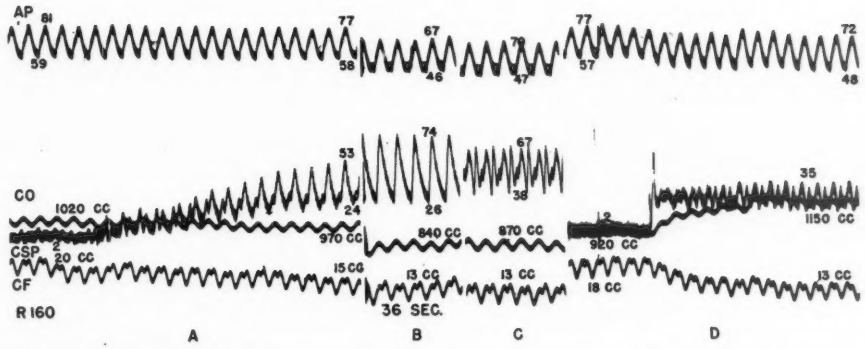

FIG. 3. Showing effects of elevation of coronary sinus pressure on left ventricular output and circumflex inflow. *A*, during coronary sinus occlusion; *B*, after 36 seconds; *C*, with occlusion of sinus outflow and connection of sinus to subclavian artery; *D*, effect of arterialization of sinus with sinus outflow open leaving an arteriovenous fistula; *AP*, aortic pressure; *CO*, left ventricular output; *CSP*, Coronary sinus pressure; *CF*, circumflex inflow.

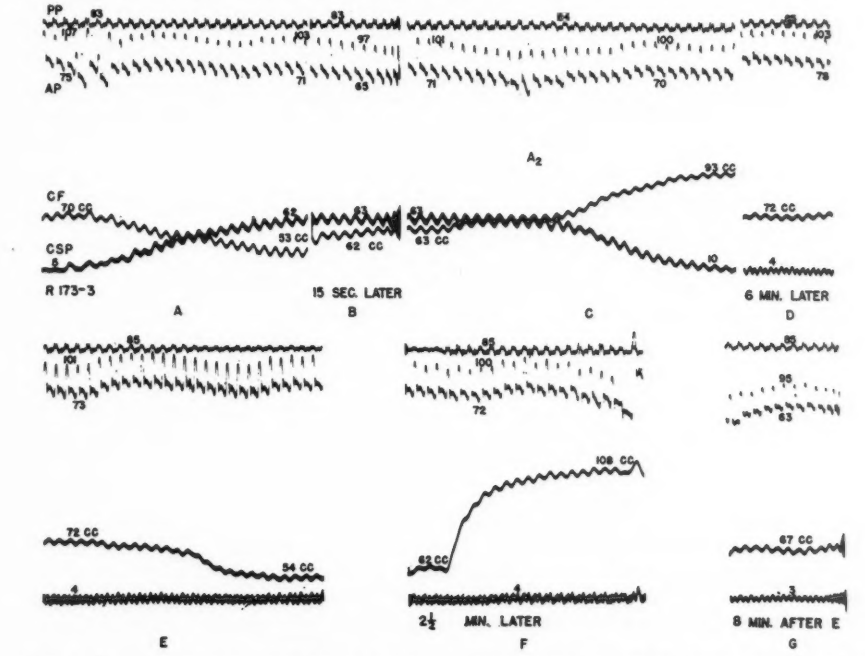

FIG. 4. Total left coronary flow before, during and after arterialization of the coronary sinus compared with responses during and after reduction of inflow with a clamp. *A*, During elevation of sinus pressure; *B*, 15 seconds later; *C*, effects of sudden reduction in sinus pressure two and one-half minutes after *A*; *D*, six minutes after *C*; *E*, during partial coronary clamping: *F*, effect of release of coronary clamp two and one-half minutes after *E*; *G*, eight minutes after *E*; *PP*, coronary perfusion pressures; *AP*, Aortic pressure; *CF*, total left coronary flow; *CSP*, coronary sinus pressure.

five measurements on four dogs there was an average increase in output of 194 cc. per minute. In each case, however, as the sinus was progressively occluded so as to elevate sinus pressure, there was a reduction in output as described above and shown in figure 3*C*.

H. Effects of Elevation of Sinus Pressure on Normal Coronary Artery Inflow

Since elevation of sinus pressure by sinus occlusion or by partial occlusion and arterialization is frequently accompanied by changes in aortic pressure, it is necessary to measure coronary flow under constant perfusion pressure in order to critically evaluate the true mechanism of flow changes. Such flow measurements were made in both the circumflex and common left coronary arteries. Figure 4*A*, *B*, *C*, and *D*, shows a typical result in the latter with arterialization of the sinus. This record shows a decrease in flow with sinus pressure elevation with recovery to near normal within a few minutes. Upon sudden release of sinus pressure the coronary flow quickly increases to even above normal and then more slowly returns to the normal. It is noteworthy that this sudden increase in flow with subsequent return to normal is identical with the coronary artery response to any temporary slight restriction of coronary flow (fig. 4*E*, *F*, and *G*). This response is due to an expansion of the coronary vascular bed as a result of some degree of myocardial ischemia.

I. Electrocardiographic Effects of Elevation of Sinus Pressure

These effects which have been recorded in lead aV_R may be divided into three groups.

1. The first group consists of the effects of elevation of sinus pressure in the presence of normal coronary artery flow. These changes have been previously described[1] and consist merely of slight to moderate flattening of the T wave with or without minor S-T segment depression. (See fig. 5, top.)

2. This second group consists of the changes produced by elevation of sinus pressure when coronary inflow is restricted. Figure 5, middle, shows that restriction of coronary inflow to reduce the mean peripheral coronary pressure to 50 mm. Hg produces no electrocardiographic

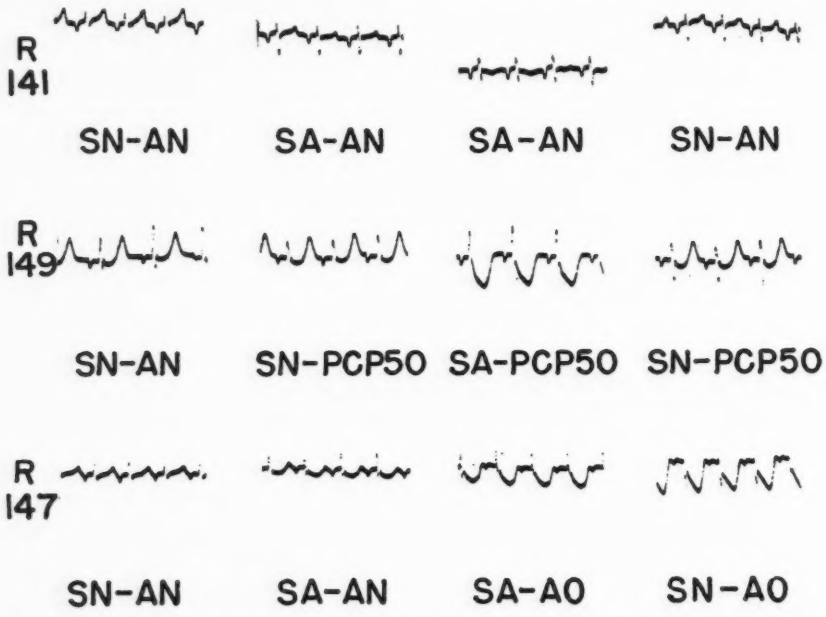

FIG. 5. Electrocardiographic effects recorded from lead aV_R of elevation of coronary sinus pressure to 50 mm. Hg. R. 141, with normal coronary inflow; R. 149 with reduction in circumflex inflow to reduce peripheral circumflex pressure (*PCP*) to 50 mm. Hg; R. 147 with complete circumflex occlusion. *SN*, sinus normal; *SA*, Sinus arterialized and partially occluded to give mean sinus pressure of 50 mm. Hg; *AN*, coronary arteries normal; *AO*, circumflex artery completely occluded.

change. However, the elevation of mean coronary sinus pressure to 50 mm. Hg results in marked S-T segment depression and T-wave inversion. The electrocardiogram returns to normal when the sinus pressure is reduced to its normal level. Many similar experiments indicate that even more severe changes occur with further reductions in peripheral coronary pressure.

3. This group consisted of studies as to the electrocardiographic effects of sinus pressure elevation after complete occlusion of a coronary artery. Figure 5, bottom, shows the typical results. The record displays the usual features produced by circumflex occlusion. Elevation of coronary sinus pressure produces unquestionable evidence of improved oxygenation of the myocardium.

On the basis of these electrocardiographic studies it is apparent that acute elevation of sinus pressure is not only ineffective, but is actually anoxating* to the myocardium in all cases except in the presence of complete coronary occlusion or drastic reduction in coronary flow.

J. Myocardial Oxygen Consumption

Although arterialization of the sinus results in retrograde capillary flow the real benefit to the myocardium must depend upon the amount of oxygen consumed by the heart. Accordingly, experiments were done to measure retrograde flow from the total left coronary with arteriovenous oxygen differences between the arterial blood entering the sinus and the venous blood escaping from the artery. The retrograde flow when back bleeding was prevented was calculated as in method 1 above. The weight of myocardium supplied by the left coronary was considered to be 85 per cent of the total heart weight.[19] In three experiments the oxygen consumptions resulting from arterialization of the sinus were 14, 24 and 25 per cent of the normal, respectively. Declining aortic pressure and cardiac dilatation during the brief periods required for collection of data showed the complete cardiac intolerance to such drastic reductions in blood supply to such a large myocardial area.

* The word 'anoxating" is used loosely to express the effects of a reducton in the blood supply to the myocardium.

Discussion

The results of these experiments serve to clarify several unanswered questions. The demonstration of a small retrograde flow with elevation of sinus pressure in the presence of complete arterial occlusion probably provides the explanation of the modification of the mortality following acute arterial occlusion previously reported.[1, 2] It is believed that although this small flow is insufficient to maintain myocardial contraction it does prevent ventricular fibrillation. Although elevation of sinus pressure increased both backflow and peripheral coronary pressure when the entire left coronary was occluded, this has never been sufficient to maintain left ventricular contraction since rapidly falling aortic pressure required the admission of blood into the left coronary artery within about one minute. The fact that retrograde flow increases with augmentation of sinus pressure and is particularly related to sinus diastolic pressure supplies the explanation to the superior benefit provided by arterialization of the sinus in contrast to the benefit resulting from complete or partial sinus occlusion. The continuous perfusion of the sinus from an artery simply provides the sinus with a higher diastolic pressure which is more favorable for retrograde flow. In accord with the findings of Heimbecker[20] on the mesentery, these experiments demonstrate that blood passing in a retrograde manner through myocardial capillaries also gives up its oxygen to the myocardium.

The question of possible benefit to the septum from elevation of sinus pressure has been investigated by injection studies. The injection of dilute India ink into the coronary sinus is well distributed throughout the entire left ventricle. In no case, however, has the central septal area showed any injection. In an effort to test further whether the septal drainage was via the coronary sinus, the septal artery was injected. In each case the central portion of the septum was injected and the injection material never appeared in the coronary sinus. It is reasoned, therefore, that in the dog the

septum could not possibly be retroperfused from the coronary sinus.

It is believed that elevation of the sinus pressure in the presence of normal coronary inflow renders the myocardium mildly anoxic. This view is supported by these observations: that coronary flow is restricted, that aortic output is reduced, that the electrocardiogram reveals a mild ischemic pattern and that there is an expansion of the coronary bed. The increase in coronary flow to above normal which occurs with reduction in sinus pressure immediately following prior elevation is by far the more sensitive indicator of myocardial anoxia or ischemia. The mechanism of such ischemia is theoretic, but is probably a result of a reduction in the normal capillary flow produced by an augmentation of pressure at the venous ends of capillaries. Under such a situation there is a loss in the pressure differential. That such capillary blockade probably occurs is evidenced by the marked electrocardiographic changes produced when identical mean pressures are applied to the coronary sinus and the coronary artery.

The decrease in backflow and the markedly hemorrhagic myocardium resulting from but a few hours of sinus pressure elevation is indeed disappointing, especially in view of the fact that mean sinus pressure was carefully limited to 50 mm. Hg. The use of large amounts of heparin may have contributed significantly. Such vascular trauma may be minimized in the more chronic dogs of Beck by virtue of the fact that the operation is done in two stages thereby producing a more gradual increase in sinus pressure. By such a technic the vessels may develop a resistance to rupture.

In conclusion it appears evident that acute arterialization of the coronary sinus renders the myocardium mildly ischemic in the presence of normal coronary circulation, but following complete and nearly complete coronary occlusion it provides a few cubic centimeters of retrograde capillary flow which serves to prevent ventricular fibrillation for at least a few hours.

Although it is tempting to make predictions based upon these studies as to the effect of chronic arterialization of the sinus as is produced in the Beck operation, it is felt that actual study of the Beck dogs is necessary. It is very questionable whether the remarkable protection described by Beck can be ascribed to the rather meager retrograde flows as found in these experiments. Three possibilities suggest themselves. Chronic sinus arterialization may: (1) produce augmentation of retrograde flow, (2) stimulate the growth of capillaries from the coronary venous system, or (3) stimulate the growth of new or pre-existing interarterial or extra coronary collaterals. Studies are now in progress to determine which if any of these possibilities are in operation.

Summary

The acute effects of elevation of coronary sinus pressure have been studied on dogs. It has been shown that the perfusion of the sinus from a systemic artery produces larger retrograde flows than those resulting from simple sinus occlusion, probably because of the higher sinus diastolic pressure. Evidence is presented which indicates that retrograde flow declines within three hours.

The studies reveal that a small retrograde flow occurs even into an occluded artery since sizeable escape routes from the artery exist. (Anterior and posterior cardiac veins.)

Elevation of coronary sinus pressure reduces left ventricular output mildly in the absence of an arteriovenous fistula and elevates output when an arteriovenous fistula is created simultaneously.

Electrocardiographic evidence shows that elevation of coronary sinus pressure results in mild myocardial anoxia in the presence of normal arterial inflow, marked myocardial ischemia when arterial inflow is reduced, and mild alleviation of the ischemia due to complete arterial occlusion.

Observations of changes in coronary flow show that elevation of sinus pressure produces a mild reduction in coronary inflow with resulting expansion of the vascular bed due to a degree of myocardial anoxia.

Studies on the amount of oxygen uptake by the myocardium resulting from arterializa

tion of the sinus is approximately from 14 to 25 per cent of normal.

The conclusion is reached that arterialization of the coronary sinus provides acute benefit to the myocardium following coronary ligation, but it is insufficient to maintain normal contraction. However, in the presence of normal or reduced coronary inflow acute elevation of sinus pressure results in myocardial anoxia probably due to restriction of capillary flow.

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Sumario Español

Los efectos fisiológicos agudos de un anastomosis de Beck de la aorta al seno coronario han sido estudiados. La evidencia presentada muestra que la arterialización del seno coronario resulta en un pequeña circulación retrógrada del seno por los capilares a la arteria ocluída y que dicha circulación retrógrada suple un 14 a 25 por ciento de la demanda normal de oxígeno del miocardio. Se sugiere que esto es insuficiente para mantener la contracción miocardica, pero probablemente evita la fibrilación ventricular. Sinembargo, cuando se arterializa el seno en presencia de circulación coronaria normal o reducida datos electrocardiográficos y de circulación coronaria muestran anoxia del miocardio. Esto probablemente se debe a la restrición en circulación capilaria y resulta en una expansión del cauce vascular coronario.

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CLINICAL PROGRESS

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The Thyroid and the Circulation

By E. COWLES ANDRUS, M.D.

GENERALLY speaking, practical knowledge of thyroid function and its circulatory consequences in health and disease has advanced by several stages. The significance of hyperthyroidism as a form of circulatory stress was recognized 165 years ago by Parry, though his descriptions were not published until 1825. Comprehension of the manifestations of hypothyroidism emerged from the early attempts to treat thyrotoxicosis by excision of the gland. The effectiveness of substitution therapy in treating myxedema was discovered in 1891 but suppression of the overactive thyroid by drugs, first with iodine, later and more effectively by thiourea derivatives, was not accomplished until several decades later. Most recently, interest has centered upon the ability of derivatives of thiourea and radioactive iodine to reduce the function of the normal thyroid gland, a property which has been grasped as a therapeutic tool in the treatment of intractable heart failure in euthyroid persons.

Particularly since the thyroid principle has been available in an injectable form, attention has been devoted to the special effects of induced hyperthyroidism upon other physiologic functions including those of the heart and circulation. Tachycardia and increased cardiac output at rest,[1, 2] exaggerated by exertion or excitement,[3] regularly follow thyroid feeding or the injection of thyroxin in animals but only after a latent period of 7 to 24 hours. Moreover, this effect may be produced in the embryo before the heart has been innervated[4] or in the heart of one animal transplanted into the neck of another when the typical effects of thyroxin are produced in the host.[5] Thyroxin has been shown to increase the rate of beating of explanted cardiac muscle cells from 2 day old chick embryos but only after 12 hours contact with the tissue.[6] Tachycardia, once provoked in the intact animal by thyroid feeding or thyroxin injection, persists in the isolated perfused heart and increases far more than normal on addition of adrenaline to the perfusate.[7] The denervated heart in situ in a hyperthyroid animal displays an exaggerated response to exercise or injected adrenaline.

The oxygen consumption of the heart-lung preparation from thyroxinized animals is measurably increased[8] as is the oxygen uptake of the isolated auricles from thyroxinized guinea pigs.[9] It has been debated whether the increased rate of oxygen consumption can be accounted for by the increased heart rate. In the heart-lung preparation it seems that this may be so, but the oxygen consumption of the isolated auricle is measurably increased even though it fails to contract. In a few instances the oxygen consumption of that portion of the human heart drained by the coronary sinus (left ventricle) has been estimated by catheterization in the presence of hyperthyroidism, and found not to be notably abnormal. In experimental hyperthyroidism, however, it seems certain that the cardiac tissue shares in the metabolic effect of the thyroid hormone, and that the tachycardia characteristic of thyroid action is due to a direct effect of the hormone, perhaps metabolic in nature, upon the heart itself.[10] In contrast, dinitrophenol, which notably stimulates metabolism, has much less influence on heart rate or none at all.

The nature of the metabolic action of thyroxin upon the body tissues is not precisely known but it can be shown to persist in an

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aqueous enzyme-containing extract of the muscle of thyroxinized animals and may, therefore, involve a change in the amount or potency of tissue enzymes.[11] Recent studies[12, 13] suggest that, by inhibiting certain enzymes which catalyze the anaerobic synthesis of high-energy phosphate compounds, thyroxin forces the metabolism of muscle into aerobic channels, requiring greater direct consumption of oxygen.

The hearts of thyroid-fed animals are heavier in proportion to body weight than those of normal controls. Because microscopic changes —intermuscular fibrosis or cellular infiltration —have been described in the hearts of some patients dying with thyrotoxicosis, the concept has been widely held in the past that in hyperthyroidism the excessive thyroid secretion exerts a specific degenerative action upon the myocardium. Rather, it seems probable that the metabolic action of thyroxin may lay the myocardium open to other nonspecific forms of injury by depleting its chemical stores. In the absence of other coexisting forms of heart disease, the changes observed are rarely significantly different in kind or degree from those in hearts of patients dying from other unrelated diseases. Goodpasture,[14] whose report of two cases is frequently referred to as indicating specific injury of the heart by hyperthyroidism, actually held the alternative view. After demonstrating that thyroxin rendered the hearts of animals unusually susceptible to injury by chloroform, he concluded that: "The evidence does not indicate that products of the thyroid alone could be responsible for the cardiac lesions which may occasionally occur in man in association with hyperthyroidism."

The overactive heart is a familiar accompaniment of hyperthyroidism in man. In many significant respects the circulation in such a patient at rest resembles that of a normal person after strenuous exercise. The heart rate is increased, the cardiac impulses are diffuse and forceful, the pulse pressure is widened and the skin capillaries are opened; the cardiac output is augmented and the entire circulation accelerated in response to the greater demands for blood created by the increased metabolic rate of the whole body. When patients with hyperthyroidism do undertake exercise, their circulatory reaction is extravagant as compared with normal persons performing the same work. In the presence of thyrotoxicosis, blood lactic acid rises excessively with effort and falls more gradually to the resting level.

The augmented circulatory demands in other tissues increase the work of the heart and the effect of excess circulating thyroid hormone seems to exaggerate the metabolic cost of that work. If not relieved by measures which diminish the output of thyroid hormone and reduce the metabolic rate, the circulatory burden may, in some instances, overwhelm the heart, provoking myocardial insufficiency. Especially remarkable, however, is the fact that, unless the cardiac reserve has already been diminished by disease, or by the natural processes of aging, the load upon the myocardium rarely becomes intolerable. The otherwise healthy hearts of persons less than 40 years of age bear the exorbitant circulatory demands of hyperthyroidism without signs of failure. In older patients, on the other hand, myocardial insufficiency may develop. This is especially true in cases of adenomatous goiter with hyperthyroidism, in which the circulatory strain, though often insidious, is frequently more protracted than in the more stormy instances of exophthalmic goiter in younger persons.

It is not surprising that the consequences of arteriosclerosis in terms of local circulatory deficiency are notably exaggerated in patients with hyperthyroidism. Angina pectoris occurs under these circumstances, and abates when the overactivity of the thyroid is curbed by appropriate therapy. In rare instances severe circulatory insufficiency in the feet, even impending gangrene, has been observed in the presence of thyrotoxicosis and relieved by iodine therapy and subtotal thyroidectomy. The circulatory requirements of the heart muscle, or of the legs, in these cases have evidently been augmented beyond the capacity of the available blood vessels by excessive thyroid secretion; when this is reduced the tissue demands can be met by the supply.

Auricular fibrillation is a common accompaniment of hyperthyroidism particularly in middle age and after. Occurring in paroxysms,

it may be the presenting symptom of thyrotoxicosis in these patients. Indeed, this irregularity, with symptoms and signs of cardiac failure, may overshadow the underlying hyperthyroidism. If the basic abnormality is searched out and appropriately treated, the results are frequently dramatic. If, on the other hand, thyrotoxicosis remains unrecognized, treatment of the cardiac status is relatively unrewarding. As an established arrhythmia, auricular fibrillation is present in over half the hyperthyroid patients with cardiac failure. Probably arising as a manifestation of increased excitability of the auricular musculature, auricular fibrillation is notably resistant to treatment in the presence of hyperthyroidism until effective measures have been taken to reduce the excess of circulating thyroid hormone.

The functional effects of the lack of thyroid hormone upon tissue metabolism are not yet completely elucidated, but it has been shown that certain tissue enzymes are decreased in amount or potency.[15] The isolated hearts of thyroidectomized animals react sluggishly to adrenaline,[16] and their denervated hearts in situ respond to exercise or to injected adrenaline with less acceleration than the normal. The normal reactivity is restored in these animals when metabolism is raised to normal levels with thyroxin.[17] Responsiveness to a variety of vasoactive drugs—adrenaline, noradrenaline, renin and angiotonin—is diminished in hypothyroid dogs with normal blood pressure, but not in animals with hypertension.[18] Capillary permeability, on the other hand, is notably increased in myxedema.[19]

In myxedematous animals the water content of the myocardium is significantly augmented and the muscle fibers show distinct degenerative changes. Gross abnormalities in the human heart in myxedema were first noted by Ord in 1880.[20] A few years later (1888) a committee of the Clinical Society of London reported on 20 autopsied cases of untreated myxedema. The hearts were examined in nine of these. One showed an early stage of interstitial myocarditis and another a comparatively advanced degree of the same.

Since the treatment of myxedema with thyroid substance was begun in 1891, only a few reports are available of detailed pathologic study of hearts of patients dying of hypothyroidism. These describe swelling of the heart muscle fibers, their sarcoplasm partly replaced by slightly granular basophilic material, and interstitial edema. Myocardial fibrosis and hypertrophy when encountered in such cases are now usually ascribed to other accompanying cardiac or vascular disease.

The cardiac enlargement often observed in these instances, which proves to be readily reversible by adequate doses of thyroid extract, unless another form of heart disease is also present, does not evidently represent true hypertrophy but rather myxedema of the heart muscle. Pericardial effusion, sometimes of considerable volume, is not uncommon in myxedematous patients and may be mistaken for enlargement of the heart. It, too, disappears under adequate replacement therapy.

The function of the heart and circulation in clinical myxedema is indolent; the cardiac output is diminished, the circulation time prolonged, and plasma and blood volumes are usually reduced.

Ellis and coworkers[21] have lately reported results of detailed hemodynamic studies in five myxedematous patients. In three, though the heart was enlarged, the pressure gradients in the central veins, right auricle and ventricle and pulmonary artery were normal. There was no clinical evidence of heart failure; cardiac output was reduced to a degree equivalent to the basal metabolism. In another case, although dyspnea, orthopnea and peripheral edema suggested myocardial insufficiency, and cardiac output was reduced out of proportion to the lowered metabolic rate, there were no measurable signs of stasis in the pulmonary circulation, heart or systemic veins at rest or with moderate exercise. Upon thyroid therapy blood flow and oxygen consumption returned to normal. In the fifth, an older patient who had had increasing dyspnea on exertion, cardiac output was also markedly reduced. Pulmonary arterial pressure and diastolic pressure in the right ventricle rose with exercise, a common accompaniment of myocardial failure. Angina pectoris on effort, inverted T waves in all leads and a prolonged QRS interval indicated that in this case coronary insufficiency and myxedema

combined to produce disability. Dyspnea abated under treatment with thyroid, but angina persisted in some degree tending to be worse with larger doses of the drug.

These carefully studied patients are representative of the variety of circulatory responses to the myxedematous state in man. Inasmuch as myxedema is predominantly a disease of middle age or after, there is a significant probability of other concurrent conditions which would decrease cardiac reserve, notably degenerative vascular disease. And yet, although the state of the heart and circulation may differ profoundly from the normal, true myocardial insufficiency is detectable only in a minority of instances in which blood flow is depressed out of proportion to the body's oxygen demands. In any event, digitalis rarely restores circulatory efficiency in these cases. The beneficial effect of thyroid therapy upon the circulatory apparatus is more likely to accomplish this even though the demands for blood flow are increased at the same time by the general metabolic effects of the hormone.

Angina pectoris as a complication of untreated myxedema has evidently occurred infrequently. Willius and Haines[22a] in a series of 162 cases of severe myxedema observed only one patient with angina. Smyth[22b] collected 578 cases from the literature among which angina had been described in only five instances, and added one more.

The occurrence of coronary insufficiency with cardiac pain in treated cases of hypothyroidism is rather more complex. In some patients with myxedema, angina appears during thyroid therapy, and doses which are tolerable to the heart in these cases may fail adequately to relieve the symptoms of hypothyroidism. In others, angina occurring during the myxedematous state is relieved following the administration of thyroid. Evidently, here as with congestive failure, the result depends upon the balance between improvement in the status of the myocardial blood flow on the one hand, and the increased cardiac work demanded by the general metabolic effects of the thyroid therapy. This should, therefore, be administered with caution, commencing with small (8 mg.) daily doses. Fatal instances of myocardial infarction during thyroid therapy of myxedema have been recorded.

The striking and often lasting relief of congestive cardiac failure or of the symptoms of coronary insufficiency in patients with hyperthyroidism when the thyrtoxicosis is reduced has led to the trial of induced hypothyroidism in the therapy of intractable heart disease or angina pectoris in euthyroid patients. Prior to the development of drugs capable of suppressing the activity of the normal thyroid, resort was had to total thyroidectomy for this purpose. The effects of this procedure in 362 patients were reported in 1937.[23] Operative mortality was 10 per cent among those with congestive failure and 5 per cent in those with angina pectoris. Sixty-four per cent of 229 patients with congestive heart failure were considerably improved, some dramatically so. In 56 per cent of 133 patients with angina pectoris, the results were excellent; in an additional 28 per cent benefit was moderate only. In the remaining patients in both groups little, if any, improvement was accomplished. In another series 13 of 15 patients subjected to subtotal thyroidectomy showed complete disappearance or marked improvement of angina pectoris for periods ranging from 8 months to 17 years.[24]

Following the application of thiouracil derivatives to the treatment of thyrotoxicosis and the demonstration that the activity of the normal thyroid[25] could be considerably depressed thereby, total thyroidectomy has been largely abandoned in favor of medical measures for inducing hypothyroidism in patients incapacitated with heart disease.[26–29] With doses of 0.3 Gm. to 0.6 Gm. of thiouracil daily some benefit can be conferred in a majority of patients with severe angina pectoris or advanced cardiac failure. Improvement, when it comes, is not to be expected within a month or often more after beginning treatment. Symptomatic response usually corresponds to the degree and constancy of lowered metabolism, although in some reported instances improvement is described without evident hypothyroidism. Though thiouracil therapy has the advantage of producing a reversible inactivation of the thyroid gland

in a significant proportion of cases it may suddenly provoke fever, granulocytopenia, or agranulocytosis. When such manifestations appear, thiouracil must, of course, be discontinued. On the other hand, some patients tolerate the drug well and in some of the reported cases it has been administered for three years or longer.

Radioactive iodine (I^{131}) which has become available from the atomic pile has recently been applied to this same purpose. While the avidity of the normal thyroid for I^{131} is less than that of the overactive gland in the patient with thyrotoxicosis, persistent hypothyroidism can regularly be induced in euthyroid patients without deterrent toxic effects, though more than half show transient signs of thyroiditis with mild elevation of basal metabolic rate within the first two to four weeks after treatment, occasionally accompanied by temporary increase in frequency of anginal attacks. In some, notably those with thyroid adenoma, repeated doses of I^{131} are required before persistently lowered metabolic rate is induced. Clinical improvement corresponds closely in time and degree with the clinical and laboratory signs of hypothyroidism, although benefit does not evidently depend upon lowering metabolism to the level of true myxedema. When this is accomplished the attacks of pain become milder, or occur only on greater effort, or orthopnea or dyspnea diminish. Blumgart,[30] whose experience with this therapy has been long and extensive, recommends that after genuine signs of hypothyroidism have appeared, thyroid be administered in doses just sufficient to maintain metabolic rate at a level of −20 to −25 per cent. Usually this requires 6 to 30 mg. per day.

Upon this regime, excellent results are obtained in about 40 per cent of cases and considerable benefit in an additional 20 per cent. Like other methods of inducing hypothyroidism, this treatment should be reserved for the severely incapacitated patients and then applied as an adjunct to other appropriate therapy. It is unlikely to be beneficial in the presence of disease causing progressive deterioration of cardiac function, such as malignant hypertension or rheumatic carditis.

Enthusiasm for this method of therapy is tempered in some quarters by concern that hypothyroidism, whether spontaneous or induced, may critically accelerate the development of atherosclerosis in systemic, or particularly in the coronary, arteries. Space does not permit a full analysis of this problem which would involve detailed review of current concepts of the biology of atherosclerosis, but it is pertinent to examine the principal sources of this concern.

Soon after the recognition of the basic connection between cretinism and hypothyroidism toward the end of the last century, it was demonstrated that total removal of the thyroid in young animals (sheep, goats and rabbits) was followed by extensive arteriosclerosis of large arteries.[31–37] These observations have been repeatedly confirmed though at least one investigator, Goldberg,[33] has been at pains to point out essential histologic differences between some of the arterial changes so produced and atherosclerosis in man.

The modern interest in the role of cholesterol in atherogenesis has focused attention upon a possibly controlling influence of the thyroid upon this process. It has been shown[38] that rabbits can be protected from the development of atherosclerotic lesions following cholesterol feeding by the simultaneous feeding of desiccated thyroid. Recently it has been demonstrated that suppression of thyroid activity with thiouracil augments the extent and severity of atherosclerosis developing in dogs fed relatively large quantities of cholesterol.[39, 40] Thiouracil feeding alone, even when continued for 15 months, although it may be accompanied by an increase of several fold in the blood cholesterol in these animals, does not cause arterial disease.[41] The role of hypothyroidism in this process appears to concern the disposal of cholesterol. Dogs can normally metabolize large quantities of this material after ingestion without accumulating high levels of cholesterol in the blood. When, however, thyroid function is suppressed by thiouracil, the ingestion of such amounts of cholesterol results in fantastically high blood levels and the arterial lesions which then

develop seem to be related quantitatively to this degree of hypercholesterolemia.

Although the literature contains some very dogmatic statements to the effect that myxedema and coronary artery disease are frequently if not invariably associated,* there are few reported instances of untreated myxedema in man in which the arterial system has been carefully and completely examined. In the report of the Committee of the Clinical Society of London to Investigate the Subject of Myxedema† the state of the arteries was mentioned in 84 cases; they were described as "atheromatous" in five. The report concludes that myxedema provokes no unusual degree of arterial degeneration. More recently in a few instances of long-standing, fatal myxedema or diminished thyroid function in aged persons, cystic degeneration of the medial muscular coat of the aorta, sometimes with rupture, has been described.[42–44] Certain other reports are impressive in presenting the picture of precocious atherosclerosis in relatively young myxedematous patients.[45, 46] In still others[47, 48] the majority of patients described were at middle age and beyond, a period when coronary artery disease is more common in euthyroid persons.

One implication does emerge from the literature dealing with atherosclerosis and myxedema which may have special significance. Bartels and Bell,‡ reporting 15 instances of coronary artery disease among 59 cases of spontaneous myxedema, found that in the women under 50 in this series coronary disease was no less common than in men. The usual ratio at this age is four cases in males to one in females. Though derived from a small number of cases the observation of Bartels and Bell possibly indicates that myxedema may diminish the sex-determined difference in the incidence of coronary artery disease in middle life.

On the other hand Blumgart, Freedberg and Kurland,[49] describing the state of the arteries in eight patients rendered hypothyroid for therapeutic purposes, report no significant differences in comparison with euthyroid patients despite lowered metabolism for 1 to 13 (average 7.4) years. The blood cholesterol in these patients had been persistently elevated and, as recently demonstrated, the lipoprotein molecules associated by Gofman with atherogenesis were measurably increased.

In summary, atherosclerosis can be produced, or its development accelerated in animals by surgical ablation of the thyroid at an early age or by the combined effects of chemical suppression of thyroid function and the ingestion of abnormal quantities of cholesterol. Opportunities for definitive studies of the vascular system in unrelieved cases of human hypothyroidism seem to this writer to have been too few to provide conclusive evidence that augmented atherosclerosis is an inevitable consequence. Without minimizing the contribution of animal experimentation to our knowledge of arterial disease, the gap between the human disease and cholesterol-induced atherosclerosis in hypothyroid or athyroid animals cannot be said as yet to have been fully bridged in all details. The athyroid state is a complex of reactive changes in several endocrine functions. The suggestive finding that myxedema may affect adversely the relatively lower incidence of atherosclerosis in the female suggests a secondary gonadal influence.

In any event, the weight of evidence indicates that the benefit conferred by induced hypothyroidism in selected cases of coronary insufficiency or myocardial failure is too real to be ignored. At the same time, it is desirable to produce the minimal suppression of thyroid function which will accomplish relief of the cardiac symptoms. It is, moreover, essential that no chance be overlooked to follow carefully cases so treated with reference to the development or progress of signs and symptoms of vascular disease intra vitam, and to conduct detailed comparison especially of the coronary vessels with those of euthyroid pa-

* For example: "Many observations indicate that, in myxedema, even when produced for therapeutic purposes, arteriosclerosis, particularly of the coronary arteries, is accelerated" (Holldack, K.: Beobachtungen am myxödemherzen. Deutsche med. Wchnschr. **74:** 16, 1949).

† Report of a Committee of the Clinical Society of London, nominated Dec. 14, 1883 to investigate the Subject of Myxedema: Supplement to vol. 21 of the Society's Transactions.

‡ Myxedema and Coronary Sclerotic Heart Disease, Tr. Am. A. for Study of Goiter, 1939.

ients post mortem. For the present it seems vise to view the procedure on the one hand as calculated risk and on the other as a special hallenge to a more complete and fruitful understanding of the pathogenesis of therosclerosis.

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CLINICAL CONFERENCES

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Recent Myocardial Infarction

Edited by EARL N. SILBER, M.D., AND LOUIS N. KATZ, M.D.

DR. LOUIS N. KATZ: The subject of this conference, recent myocardial infarction, is timely, for the attitude still prevails that, except perhaps for anticoagulant therapy, the management of coronary occlusion is essentially unchanged from that of Herrick's day when infarction was first recognized as an important clinical entity. Our purpose today is to re-examine the problems incident to myocardial infarction and, if possible, to arrive at a judgement of what constitutes appropriate therapy in the light of modern concepts of the pathogenesis and pathophysiology of this disease. It would seem appropriate to initiate this conference by discussing briefly current thinking with respect to the pathogenesis of coronary arteriosclerosis. Dr. Stamler would you comment on this aspect of the problem?

DR. JEREMIAH STAMLER: At the outset it is essential to emphasize that we are dealing here with atherosclerosis, the most important among the several disease entities which together comprise the generic grouping arteriosclerosis. At least 90 per cent of all myocardial infarctions are atherosclerotic in origin. Today the long prevalent attitude that atherosclerosis is a physiologic process of aging has been irrevocably rejected. At the same time, the majority of investigators studying the pathogenesis of this disease are in agreement on a general approach which may be designated the cholesterol-lipid-lipoprotein concept of atherogenesis.

In support of this concept are morphologic and biochemical observations which demonstrate that abnormal accumulations of cholesterol-lipid material characterize atherosclerotic lesions. Furthermore, lesions resembling human atherosclerosis have been produced experimentally in animals only by cholesterol feeding. An exception to this is the estrogen-induced atherosclerosis in the chick. Lastly, there is significant clinical evidence supporting the cholesterol concept. Diseases accompanied by hypercholesterolemic hyperlipemia—for example, diabetes mellitus, the nephrotic syndrome, myxedema, and familial (hypercholesterolemic) lipidosis—are associated with a high incidence of premature atherosclerosis.

In recent years it has been appreciated that persons with significant coronary atherosclerosis, particularly in the middle decades of life, usually exhibit a hypercholesterolemic tendency. The relationship between plasma cholesterol-lipid levels and coronary atherogenesis has been amplified by studies relating to the state of aggregation of plasma cholesterol; thus, ultracentrifugal analysis of blood lipids suggests a significant correlation between the emergence of abnormal classes of lipoproteins in the plasma and the development of clinical manifestations of atherosclerosis.

There is, moreover, circumstantial evidence suggesting that the varying incidence of atherosclerosis among ethnic groups tends to correlate with differences in dietary habits, with respect to the ingestion of animal products containing cholesterol and lipid. These findings do not necessarily imply a direct correlation between diet and atherogenesis; marked differences obviously exist in any given population with respect to the atherogenic response to a high cholesterol–high lipid diet. In the final analysis, it appears that within the endogenous lipid metabolism of the individual are the crucial

This paper is derived from a Joint Conference of the Cardiovascular and Medical Departments of the Michael Reese Hospital, Chicago, Ill.

factors determining atherogenic response to chronic ingestion of high cholesterol–high lipid diets.

DR. KATZ: Dr. Stamler's opening remarks on pathogenesis serve as an appropriate background for consideration of the clinical problems incident to myocardial infarction. Such discussion, I think, is best stimulated by a consideration of the clinical features of a specific illustrative case. For this purpose I have asked Dr. Becker, one of our senior residents in medicine, to present briefly the case history of a recent patient; this case aroused a great deal of interest among the hospital staff because of the complications which accompanied it and their therapeutic management.

DR GERALD BECKER: The patient, a 62 year old pattern maker, was admitted in stupor to the medical service of Michael Reese Hospital. Two hours earlier, at home, he had been seized with a vise-like substernal pain of excruciating severity, had vomited several times, and collapsed. No other history was obtainable.

Examination revealed a stout, middle-aged, semiconscious male, whose skin was pale, cold and clammy. The pulse was thready, with a rate of 30. No blood pressure was obtainable. The heart sounds were diminished and of poor quality. An electrocardiogram at that time revealed auricular fibrillation with either an almost complete or a very advanced second degree A-V block. The marked S-T segment depression in leads I, aV_L and the precordial leads and the marked elevation of S-T segments in leads II and III were indicative of a recent posteroseptal infarct.

Within 30 minutes after the patient was admitted to the hospital an intra-arterial transfusion of whole blood was initiated. Within 10 minutes after the start of the infusion, the patient's blood pressure was obtainable at 60/0 mm. Hg and his sensorium had improved. At the end of 20 minutes during which 300 cc. of blood had been administered, the patient's blood pressure was 90/60 and he was rational. In the next five minutes an additional 200 cc. of blood were infused, at the end of which time the patient's blood pressure was 130/70. One hour later the patient's pulse was 50 and his blood pressure 140/90; four hours later the patient's cardiac rhythm converted spontaneously from auricular fibrillation to sinus rhythm.

Despite the prompt restoration of his blood pressure to normal limits, the patient was oliguric for the next five days and exhibited transient retention of nitrogenous products. On the fifth day after admission he developed abruptly an episode of tachycardia and became tachypneic and restless. An electrocardiogram revealed auricular fibrillation with a rapid ventricular rate and changes in contour of the ventricular complexes pathognomonic of recent healing infarction of the posterior wall of the left ventricle. The appearance of distended neck veins, of coarse rales at the lung bases bilaterally and of dyspnea led to the decision that the patient should be digitalized. This was effected in the next eight hours and was attended by slowing of the patient's ventricular rate and by marked subjective improvement. By the next morning, the patient's cardiac rhythm had reverted once again from auricular fibrillation to a sinus rhythm.

The remainder of the patient's course in the hospital was uneventful and he was discharged 46 days after admission without need for digitalis or other cardiac medication. It is now two years since that episode and the patient has remained well; he has not experienced angina pectoris or congestive cardiac failure.

DR. KATZ: Thank you Dr. Becker. In a case such as this one where initial information is scant the electrocardiogram has its greatest sphere of usefulness, making possible prompt diagnosis and appropriate therapy. Dr. Pick would you comment on the electrocardiographic aspects of myocardial infarction?

DR. ALFRED PICK: It can be anticipated that in about two thirds of patients with recent infarction due to occlusion of a main coronary artery changes pathognomonic of the lesion will develop in the electrocardiogram. Marked deviations of the S-T segment above and below the isoelectric line occur during the transient stage of severe myocardial injury, which is preceded sometimes and followed usually by profound alterations in the contour of the T wave, reflecting the disturbances of ventricular repolarization which attend protracted myocardial ischemia. Depending on the degree, the duration, and the extent of this functional alteration, myocardial necrosis frequently develops which in turn changes the nature of the forces produced during ventricular excitation (depolarization) and can be recognized in the electrocardiogram by alterations of the QRS complex, and especially by the appearance of deep Q waves. The chronologic evolution of all these changes in certain leads and their reciprocal pattern in others, is sufficient to confirm the clinical impression of myocardial infarction, and to localize the

lesion to the anterior, diaphragmatic (posterior), or lateral wall of the left ventricle.

In about one third of those individuals suspected of having recent myocardial infarction, electrocardiographic changes are atypical or absent. In this group appear patients with pre-existent electrocardiographic anomalies like left bundle branch system block, or A-V block with an idioventricular pacemaker below the bifurcation of the A-V bundle, patients with marked left heart strain, and, not infrequently, individuals with previous myocardial infarction. All these conditions may produce such marked alteration of ventricular activation and deactivation as to "mask" the usual changes expected with recent myocardial infarction. In such cases, confirmation of the clinical diagnosis should be sought in serial tracings which may reveal some progressive, although not typical, changes of the electrocardiographic pattern. Of course, a negative electrocardiogram does not exclude recent myocardial infarction.

A second atypical group is represented by patients in whom the expected electrocardiographic pattern does not develop to its full extent and/or persists for only a short period of time. QRS alterations may be insignificant or absent if myocardial necrosis does not involve the entire thickness of the ventricular wall and remains restricted to its subepicardial or subendocardial layers, or if islands of viable muscle remain within areas of necrosis. If the occluded vessel is small and collateral circulation well developed, necrosis may be entirely absent and only S-T segment–T-wave alterations will appear in the electrocardiogram, persisting for a relatively short time and followed quickly by complete restitution to the previous more or less normal pattern. Such episodes may occur repeatedly preceding, and sometimes also subsequent to, a severe attack revealing the classical electrocardiographic picture. From the electrocardiographic standpoint, such instances have been variably designated by such terms as: "acute (protracted) coronary insufficiency," "acute coronary failure," "impending myocardial infarction," or "atypical myocardial infarct." In summary then, recent myocardial infarction, diagnosed on clinical grounds, is frequently, but not invariably, associated with a characteristic electrocardiographic pattern. While a single tracing may strongly suggest such a diagnosis, the final judgement should be based on the type of evolution seen in serial electrocardiograms. This will also help to distinguish this condition from acute cor pulmonale, acute pericarditis, acute myocarditis and the like, which may imitate recent myocardial infarction. Our practice is to recommend a repeat electrocardiogram in two days and then at progressively longer intervals, at first four days, then one week and two weeks, until stabilization.

I deliberately omitted discussion of the disturbance of conduction and rhythm which were a prominent feature of this case, and I would like to invite comment from Dr. Langendorf with regard to this problem.

DR. RICHARD LANGENDORF: Hypoxia has a profound effect on the fundamental properties of the cardiac muscle. It increases its irritability and decreases its conductivity. Thus, it is not surprising that disturbances of both formation and conduction of the cardiac impulse are frequently observed during the acute stage of myocardial infarction. As a rule, the former, that is, premature systoles and paroxysmal tachycardia, constitute the more serious disturbance and call for immediate treatment, because they increase the work of the heart and at the same time enhance the coronary insufficiency as a result of poor ventricular filling. Under the circumstances, a relatively mild disturbance like ventricular premature systoles is more prone to develop into a more serious one, namely ventricular paroxysmal tachycardia, or may even be a forerunner of fatal ventricular fibrillation. Such a development is more common than that of a dangerously slow ventricular rate or ventricular standstill as a result of block of A-V conduction.

Premature systoles, particularly if they occur frequently, if several of them occur in succession, or if the electrocardiogram demonstrates their multifocal origin, should be eliminated by the use of antiarrhythmic drugs like quinidine or procaine amide. If oral medication is feasible 0.4 to 0.6 Gm. of quinidine sulfate

or 500 to 750 mg. of procaine amide should be given every two to three hours, depending on the result of frequent electrocardiographic observation. If oral administration is not possible or if a more rapid effect is desired, as in the case of paroxysmal tachycardia, one has to resort to intramuscular or even intravenous administration of the drugs, in which event the use of procaine amide would appear safer than quinidine. In the presence of a supraventricular tachycardia, including auricular fibrillation and auricular flutter, digitalis (orally or intravenously) or strophanthin (intravenously) can be used to slow the ventricular rate as was done in the case under discussion. It seems to us that in the supraventricular tachycardias digitalization is safer than quinidine or procaine amide therapy and should be used particularly in the case of auricular flutter where initial treament with quinidine or procaine amide may be followed by a very rapid ventricular rate due to 1:1 A-V conduction.

The occurrence of A-V block, as in this instance, is quite common in the early stages of posterior wall infarction. It may vary between simple prolongation of the P-R interval and second degree A-V block with nodal escapes; even in its more advanced forms A-V block tends to be a transient phenomenon which does not call for any special therapeutic measures. In advanced second degree A-V block, an A-V nodal pacemaker with a rate of about 50 tends to take over, giving the impression of complete A-V block; actually, complete A-V block with a very slow ventricular rate (less than 30) and an idioventricular pacemaker arising below the bifurcation of the common bundle is much less common and Adams-Stokes attacks during temporary ventricular standstill are quite uncommon in recent myocardial infarction. A recent report would suggest that in such an event isopropyl norepinephrine (Isuprel) would be the drug of choice.

I should like to point out two common mistakes in diagnosis of the arrhythmias accompanying recent myocardial infarction which may easily lead to errors in medication.

(1) Supraventricular tachycardias may be mistaken for tachycardias of ventricular origin. This is particularly true for auricular fibrillation with a rapid ventricular rate and aberrant ventricular conduction in the electrocardiogram. This mistake may lead to digitalis being withheld.

(2) "Bigeminal rhythm" diagnosed at the bedside may be considered an indication for quinidine therapy under the assumption that the arrhythmia is due to ectopic impulse formation; actually, in our experience, "bigeminal rhythm" in acute myocardial infarction—notably with posterior wall involvement—is more often due to persistent 3:2 A-V block than to premature systoles. An electrocardiogram will immediately disclose the true nature of the arrhythmia which in the case of 3:2 A-V block presents no indication for special therapy and a contraindication for the use of quinidine.

DR. KATZ: Thank you Drs. Pick and Langendorf.

A PHYSICIAN: What about atropine, papaverine and Khellin?

DR. KATZ: I never was excited about atropine for arrhythmias, and I have lost my early enthusiasm for papaverine and Khellin.

AN INTERNE: Isn't the use of digitalis hazardous in the presence of myocardial infarction?

DR. KATZ: This is an important question which I would like to have answered by Dr. Brams, who has had a great deal of practical experience with this aspect of the problem.

DR. WILLIAM A. BRAMS: The use of digitalis in acute myocardial infarction is still controversial in some quarters. The untoward results which have in the past been erroneously attributed to its use in such a situation are now generally agreed to be part of the grave picture presented by patients who require digitalis rather than the result of the action of the drug, per se. To be sure, it should not be used in all cases. Digitalis is necessary if congestive heart failure develops and in cases of auricular fibrillation with rapid ventricular response which do not revert to sinus rhythm either spontaneously or after quindine.

In general, the treatment of congestive heart failure complicating recent myocardial infarction is no different than its treatment under other circumstances. The dosage of digitalis will depend upon how soon after the

onset of myocardial infarction its use is contemplated and upon the severity of the congestive heart failure. There are no problems in the use of digitalis if congestive failure occurs after the patient is ambulatory. I prefer, as a rule, either digitoxin or Digoxin, orally, 2.0 mg. of the latter or 1.2 mg. of the former as an average initial dose if no digitalis has been used before. The next day 0.5 mg. of Digoxin or 0.3 mg. of digitoxin may be given and the subsequent dosage is governed by the results. Intravenous administration is avoided unless it is thought that absorption will be poor or there is vomiting or diarrhea. If congestive heart failure develops shortly after the onset of myocardial infarction or while the patient is still in bed one half of the foregoing dosage may be used initially. This dose is repeated the next day and maintenance dosage is again regulated by the results, usually 0.25 to 0.5 mg. of Digoxin or 0.1 to 0.2 mg. of digitoxin daily will suffice.

DR. KATZ: Thank you Dr. Brams. I am delighted that you stressed the similarity of congestive failure occurring with myocardial infarction with that complicating other forms of heart disease.

The outcome of therapy in patients in whom myocardial infarction precipitates shock has been extremely discouraging, the mortality ranging from 50 to 95 per cent. I should like to call on Dr. Silber for a discussion of the management of this complication as exemplified in this patient. Dr. Silber has had considerable experience in this regard.

DR. EARL SILBER: The basis for the development of shock in acute myocardial infarction is not fully understood. Undoubtedly of primary importance is the abrupt fall in cardiac output, but peripheral vascular collapse is a second significant factor. Other mechanisms are probably operative, but are at present obscure. Severe shock carries with it certain grave consequences in myocardial infarction. Coronary flow, it will be recalled, depends upon mean aortic pressure and the cardiac output. A sharp decline in these two factors not only may favor the development of more extensive infarction, but may exert a deleterious effect on the contractile power of the viable muscle. Studies of the shock state by a variety of methods all point to progressive deterioration of the myocardium under such circumstances. This depression, if uncorrected, leads to irreversible changes.

Cerebral ischemia associated with a decline in cardiac output may of itself operate to intensify the shock state by depression of vital centers. Finally, marked diminution in renal blood flow leads to ischemia and renal tubular damage. If shock is prolonged, "lower nephron" nephrosis may develop even after a normal blood pressure has been restored.

Obviously then the basis of treatment rests with measures which have as their purpose the prompt restoration of an effective blood pressure. Today there are two ways to accomplish this: (1) transfusion and (2) vasopressor drugs.

A myocardium weakened and herniating owing to insufficient blood supply may show a prompt return toward normal with the addition of plasma or blood; this may be most effectively accomplished by intra-arterial transfusion which makes possible effective perfusion of the coronary arteries and cerebral circulation with a relatively small amount of blood. By improving coronary flow for a short period of time in this manner, it appears from our limited experience that hypoxia is relieved and there is a tendency for restoration of normal contractile power to that part of the myocardium that has not been infarcted.

Where shock is not severe, the use of vasopressor drugs such as norepinephrine, which in physiologic doses acts primarily on the peripheral vascular mechanisms rather than as a cardiac stimulant, may be the treatment of choice. It must be remembered that when blood pressure is maintained by vasoconstriction rather than by augmented cardiac output, tissue flow diminishes; under these circumstances, tissue necrosis and further decline in renal function may result. Both have been observed. Moreover when large amounts of pressor drugs are required to effect a rise in blood pressure, the pharmacologic difference between these various agents largely disappears. Therefore, when there is no obtainable blood pressure, pressor drugs would not appear to be the treatment of choice. Under

these circumstances intra-arterial transfusion followed by norepinephrine to sustain the pressor response obtained by the former may be the most effective approach to the problem.

By the very nature of the lesion no method of treatment can hope to provide a consistent result. Considerably more work remains to be done before any method of treatment of shock can be finally evaluated.

DR. KATZ: Thank you Dr. Silber. I wonder whether or not you are in general agreement with Dr. Silber on the basis of your experience, Dr. Miller?

DR. ALBERT MILLER: In general, yes. Experimental evidence suggests that under certain circumstances a drug like norepinephrine may by virtue of its pressor effect improve coronary flow and thereby act like an intra-arterial transfusion. Vasopressor drugs can often raise blood pressure from unobtainable levels and hold it at or near normal. The advantage of norepinephrine over the older drugs like epinephrine, ephedrine and Neosynephrine in the treatment of shock is now clear.

Dr. KATZ: It is a pleasure to have such unanimity of opinion.

A PHYSICIAN: Is it possible that the severe pain of infarction leads to shock?

DR. KATZ: Anything is possible. I believe that the severe pain here as in any other circumstances can cause peripheral vascular collapse and may precipitate shock. Sometimes patients show marked restlessness before shock develops. It is for such restlessness, as well as for extreme pain and dyspnea, that sedation is particularly valuable. This brings to mind the fact that the addition of oxygen therapy may on occasion relieve pain where other measures have failed. In addition, I believe that oxygen is indicated whenever there is evidence of pulmonary engorgement which may interfere with the transfer of oxygen across the alveolar-capillary membrane. Oxygen should not be used routinely but only when there is a specific indication. Unless there is acute pulmonary edema, when a mask is indicated, a good tent is preferred. The patient and his family should, of course, be informed that oxygen is no longer "a last ditch measure."

NORTHWESTERN UNIVERSITY STUDENT CLERK: Was anticoagulant treatment used in this patient?

DR. BECKER: I neglected to say so, but the patient was "dicumarolized" the day after admission and anticoagulant therapy maintained until about a week before discharge from the hospital, which was the time ambulation began.

DR. KATZ: Anticoagulant therapy, I think, has been established as an integral part of therapy in myocardial infarction, and it is unnecessary to belabor the point much beyond reiterating that anticoagulants effect an appreciable reduction in the occurrence of thromboembolism and extension of infarction; our departmental opinion recommends its routine use except where specific contraindications exist. In fact I believe heparin should be used in conjunction with Dicumarol (or Tromexan) and the latter must be controlled by adequate prothrombin times. Really, we do not know the exact mechanism of Dicumarol action and I must emphasize that we are still a long way from the ideal anticoagulant.

Dr. Mack you have always emphasized the emotional impact that accompanies myocardial infarction and the enforced restriction incident to it. Would you comment on bed rest and recent trends which have redefined rest as we have been accustomed to think about it in the treatment of recent infarction?

DR. IRVING MACK: There can be no doubt that rest is one of the most important single procedures in the total therapy of a patient with a recent myocardial infarct. However, the concept of rest which has developed is a distorted one, often quite removed from the original purpose, namely to keep the work of the heart at a minimum. The usual instructions seen on the hospital chart of such a patient are: "absolute bed rest; to be fed by the nurse." As a result we find the patient kept in a state of mummy-like immobility, warned against any movement, lying helpless with all the fear such absolute restraint instills, plus the cultural fear associated with the gravity of a "heart attack." Such complete immobility is highly unphysiologic because it predisposes to phlebothrombotic phenomena.

to the development of a rapid deterioration in the "physical condition" of the patient, and to the removal of the mechanism of release of emotional tension through motor activity. To aggravate this insult by forcing the patient to use a bed pan in the recumbent position is unforgivable. Although well recognized by most physicians, it apparently took a recent complex study to demonstrate that the energy expended by the body as a whole, and hence by the heart also, was greater during the use of the bedpan than with the use of a bedside commode. In addition most patients may be permitted to feed themselves if the bedside tray table is properly constructed. Recently it has been advocated that rest in a comfortable lounge chair with wide arms was preferable to constant recumbency. Indeed, in the presence of congestive heart failure, this type of rest is usually associated with a decrease in the load of the heart and an amelioration of symptoms. Sleeping and frequent naps, of course, are usually more comfortably indulged in while in bed, but during the day the patient may spend much of his time sitting in this easy chair at the bedside. It is preferable to move the patient in and out of bed, at least at the beginning, rather than have him do so himself. The above procedures combined with the proper reassuring attitude on the part of the physician will probably result in a reduction in the amount of narcotics required and a smoother convalescence.

However, modifications of the above regime are mandatory if certain complications are present. For example, if a marked fall in blood pressure or actual cardiogenic shock is present, the recumbant position is necessary to maintain cerebral blood flow. Likewise, if thromboembolic phenomena are present, more strict limitations are also indicated.

It should be clearly understood, therefore, that this is not a recommendation for the abolishment of bed rest nor the abridgment of the period of rest; it is a plea for a more intelligent use of technics which guarantee a more restful type of rest.

After healing of the infarct has occurred, what then with regard to long-term restriction of activity? Certainly a patient with coronary sclerosis should have some restriction of activity probably for the rest of his life; heavy labor and strenuous competitive sports should be avoided. However, usually this does not mean retirement. Such a person is usually capable of resuming his occupation with a sensible slowing of his pace. It is the pace not the job that matters most. There has never been any evidence that extreme restriction of activity with its resultant invalidism can prevent the progress of atherosclerosis in the coronary arteries, or prevent a coronary occlusion. However, if complications, such as congestive failure or frequent anginal pain appear, much more drastic limitation of physical activity does become necessary.

It is clear that as physicians we must be honest with ourselves and our patients. It is to be feared that the gradual development of the doctrine of extremely strict bed rest after a recent myocardial infarction, and the fantastic curbs on the activity of such a patient for the rest of his life, have their origin in the irrational fears of the physician and of the patient's family that, were another coronary occlusion to develop, or were the infarct to extend, "absolute" bed rest would have prevented them. There is no basis for such magical irrational attitudes, and it is our duty to educate ourselves and our patients to the more logical regime of rest as outlined above.

DR. KATZ: Thank you Dr. Mack. You imply that serenity on the part of the patient and avoidance of "nagging" by the patient's family and friends are more beneficial than worry and misguided good intentions.

CARDIOVASCULAR FELLOW: What about smoking and drinking?

DR. KATZ: I would ask the patient with coronary disease to stop smoking for two weeks and if he feels better, he himself will continue to refrain from it. Scientifically the effect of smoking has not been established. Tobacco angina is rare. I think drinking is good if in moderation and the person has no contraindication to its use, including, by the way, the person who becomes worse and could become a chronic alcoholic. This all applies to the period after convalescence.

DR. JAKUB SCHLICHTER: May I offer an

addendum to Dr. Mack's comments on rest which I think is pertinent to this problem?

DR. KATZ: You are referring, I presume, to the facts brought to light by the recent departmental analysis of the problem of ventricular aneurysm?

DR. SCHLICHTER: Yes. One of the sequellae of myocardial infarction is ventricular aneurysm. The incidence at autopsy of ventricular aneurysm at Michael Reese Hospital was 1.8 per cent of all cases or 20 per cent of all cases with myocardial infarction. A total of 102 cases were analyzed.

A vital factor facilitating the formation of cardiac aneurysm seems to be large through and through infarction. Frequently, however, muscle fibers can be seen in the aneurysmal sac, forming half of the thickness of its wall. Half of the cases showed pericarditis. A large infarct is not inevitably a forerunner of aneurysm formation.

As important as the anatomic background, is the stress to which the heart is subjected during the early stage of infarction. In our series, the increased load put upon the left ventricle at this time was revealed (1) by early unwarranted ambulation, (2) by systemic hypertension, and (3) by the anatomic deformities of the valves or aorta.

Acute aneurysm can be observed as early as two days after infarction; chronic aneurysms were seen one month after coronary occlusion.

One of the outstanding sequellae of ventricular aneurysm is the more frequent occurrence of mural thrombi and the consequent greater incidence of thromboembolic phenomena. Because of these two factors ventricular aneurysm carries with it a much poorer prognosis statistically then does myocardial infarction without aneurysm.

In spite of the frequency of thromboembolism, the most common cause of the terminal illness and death was congestive heart failure or recurrent myocardial infarction.

The chief diagnostic features of ventricular aneurysm include (1) evidence of a large myocardial infarction and (2) demonstration of a localized bulge of the heart (with paradoxic pulsation) by radiographic methods. Physical signs and symptoms may be suggestive but not conclusive. Electrocardiographically, the residual pattern of myocardial infarction, the persistent S-T deviations and the small R_1, deep S_2 and S_3 pattern should keep the observer alert to the possibility of aneurysm of the ventricle.

I would make the following suggestions for therapy: (1) The prohibition of early ambulation in the presence of hypertension, valvular deformities or severe illness suggestive of large, through-and-through infarction should be mandatory. (2) The institution of anticoagulant therapy at once following diagnosis of myocardial infarction. This should be continued through the entire course of bed rest. (3) Vigorous attack upon the early manifestations of congestive failure.

Ventricular aneurysm is not to be dismissed lightly since it definitely carries with it a shortened expectancy of life and a greater tendency to superimposed illnesses as compared with myocardial infarction without aneurysm.

DR. KATZ: Thank you Dr. Schlichter for your important contribution. No discussion of therapy today would be complete without mention of dietary management. Dr. Rodbard who has been a major figure in the team that is pursuing this problem in our laboratory is here and I wish he would comment on this subject.

DR. SIMON RODBARD: In view of recent advances further demonstrating a relationship between dietary cholesterol and atherosclerosis, experimental and clinical, it would be well for the practicing physician to note and possibly apply some of the newer knowledge. Certainly, one cannot prove beyond question today that cholesterol ingestion causes coronary disease in man, although there are many straws in the wind to support this thesis. Yet inspection of hospital menus reveals a remarkably high cholesterol content of the diets prescribed for patients with recent infarction. In these diets, breakfasts, as I have observed, almost always contain two eggs, cream and butter. Lunches and suppers are similarly high in cholesterol. It would seem sensible to suggest, even on the

basis of the incomplete proof available at present, that high cholesterol diets should be avoided, at least in the immediate postinfarction period. This regimen would certainly not injure the patient in any way, and until the guilt by association between cholesterol and atherosclerosis is dispelled, it would be the better part of discretion to avoid cholesterol at such a critical period. Moreover, recent preliminary studies suggest that with reduction of abnormally elevated plasma lipid–lipoprotein levels by means of low cholesterol–low fat diets, the recurrence rate of myocardial infarction may be lowered. The final answer to all this must await further study.

Other dietary considerations also demand attention. The high cholesterol diets of infants and children have long been offered as proof against a relationship between cholesterol ingestion and atherosclerosis. However it now has become clear that the age of the patient plays an important part in his response to a cholesterol diet. The pattern of ingestion also is important. The ingestion of cholesterol day in and day out provides a much greater atherogenic stimulus than does the ingestion of equal quantities taken in bursts, with intermittent periods of respite from this material. Finally other factors in the diet affect absorption of cholesterol. Fats and oils aid absorption. Of real importance is the recent finding that the addition of plant sterols to the diet results in an inhibition of absorption of dietary cholesterol. These results are potentially of great importance in the control of atherosclerosis and deserve further consideration.

An Interne: Are lipotropic agents useful in the treatment of atherosclerosis?

Dr. Stamler: The extravagant claims that lipotropic factors are useful in the prophylaxis and therapy of human atherosclerosis are without foundation in either experimental or clinical research. I should also like to add one word about the use of heparin at this time and that is the available evidence is still too inadequate to permit inclusion of this drug in the therapeutic armamentarium of atherosclerosis and its complications.

Dr. Jack Golden: There has been considerable excitement around Michael Reese Hospital recently concerning estrogens and atherosclerosis. Where do these hormones fit into the picture?

Dr. Katz: Dr. Pick, this is work with which you are intimately concerned. Would you answer Dr. Golden's question?

Dr. Ruth Pick: Until recently, the well known sex differential in susceptibility to human coronary atherosclerosis was an intriguing enigma. The last year or two has witnessed new work which may significantly clarify the whole problem. In this laboratory it has been shown that estrogen affords a high degree of immunity to experimental cholesterol-induced coronary atherogenesis in cockerels. Moreover, this hormone is effective both therapeutically and prophylactically in this species. It not only inhibits coronary atherogenesis in cholesterol-fed chicks, but reverses previously induced lesions. These results suggest that estrogenic function in the human female prior to the menopause may be a key factor in the immunity of women to coronary atherogenesis. Other work recently appearing in the literature further indicates that estrogenic hormone influences plasma lipid-lipoprotein levels and atherogenesis in human beings. All these findings suggest an additional new path to a possible mode of therapy in man. Undoubtedly the next few years will witness intense research activity along these lines which will more definitively clarify the relationship of estrogen to atherogenesis in man and experimental animals. A hint has recently been obtained in the chick that the feminizing effect of estrogen can be neutralized by androgen without abolishing the anti-atherogenic action of estrogen.

Dr. Katz: We are now testing this in man. Because the remaining time is short I shall ask Dr. Golden to close the discussion by pointing up for this audience the outlook for survival in a patient who has suffered recent myocardial infarction.

Dr. Golden: Because of the many variable factors involved, an attempt to estimate the duration of life of an individual patient with recent myocardial infarction is extremely diffi-

cult and impractical. Analyses of data from large series of cases have yielded certain generalizations. In the absence of serious complications during the first two or three weeks, most patients do recover from the initial attack. Reports of immediate mortality vary from 15 to 25 per cent. The reduction of thromboembolic hazards and the improved control of complicating infections have favorably influenced the outlook for recovery.

Life expectancy after recovery varies greatly. The average duration of life is said to be about three to four years; but I understand from Dr. Katz that in a recent survey of patients at this hospital who had suffered their first infarction in the 10 year period 1932–1942, almost 50 per cent survived from 5 to 20 years and three-fourths of these lived 10 to 20 years. This is really encouraging. Longevity is unfavorably influenced by such factors as advanced age, repetition of infarction, cardiac failure and the presence of hypertension, diabetes mellitus and associated heart lesions. Myocardial infarction still remains the greatest scourge of human society in men in their productive years.

DR. KATZ: Thank you Dr. Golden. Time has a habit of running out and we must close. By way of summary, let me recapitulate briefly what has been brought out in the conference this morning: The basis for myocardial infarction is almost exclusively coronary atherosclerosis. The evidence is overwhelming that these lesions are in some way related to endogenous cholesterol metabolism controlled by hormones. The electrocardiogram is vital to diagnosis and to appropriate recognition and management of associated arrhythmias. Improved treatment of the shock state by intra-arterial transfusion and vasopressor drugs promises to reduce the early mortality but this is still a grave complication. Our concepts of rest in this disease are undergoing a more sensible evolution, but a conservative attitude must still be pushed. Low cholesterol-low fat diets and estrogen therapy are the most promising developments in the field. Surely there is no doubt that obesity is harmful.

We have every reason to hope that we are on the threshold of a major advance in the control of a disease which, at present, accounts for the major loss to society of individuals in their most fruitful period of life.

ABSTRACTS

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AVITAMINOSIS

Griffith, R. L.: Condition of the Heart Following Beriberi and Malnutrition. Arch. Int. Med. **89:** 743 (May), 1952.

The condition of the heart was evaluated on 109 men who had suffered from beriberi and severe malnutrition during the 44 months they were Japanese prisoners of war. Patients with beriberi who survived the acute stages of the disease and who were properly treated did not have residual clinical heart disease from the beriberi. Among patients who have recovered from beriberi the incidence of cardiovascular disease from other causes is probably no higher than would normally be expected.

It is possible that in some patients subclinical microscopic changes in the myocardium may persist after the beriberi. It is also possible that, as a result of chronic alcoholism or some other continued nutritional deficiency, the acute stages of beriberi heart disease may be protracted or recurrent, and heart failure may occur late in the disease. Such patients probably have not been adequately treated and should be considered as having prolonged acute beriberi heart disease rather than residual heart damage. It did not appear that the 44 months on low-calory, low-fat diets decreased the incidence of arteriosclerosis in these men.

BERNSTEIN

BACTERIAL ENDOCARDITIS

Dowling, H. F., Lepper, M., Caldwell, E. R., and Spies, H. W.: Staphylococcic Endocarditis: An Analysis of 25 Cases Treated with Antibiotics, Together with a Review of the Recent Literature. Medicine **31:** 155 (May), 1952.

The authors point out that staphylococcic endocarditis is second in frequency only to streptococcic endocarditis. In the recent literature the relative frequency is 1 to 2.6. Staphylococci which have hitherto been regarded as nonpathogenic can cause endocarditis; for instance, *Staphylococcus albus* and coagulase-negative organisms constitute a large minority of infecting organisms. One reason for the recent apparent increase of staphylococcic infection may be the practice of self-injection intravenously by narcotic addicts. Other predisposing factors include infections of the skin and subcutaneous tissues, dental infections, osteomyelitis and other infections.

The valves attacked were previously involved by rheumatic fever in about half the cases, and were apparently healthy in the remainder. Mitral involvement was most common (60 per cent), aortic and tricuspid about half or one-third as frequent, and pulmonic involvement rare. Tricuspid involvement was particularly common in narcotic addicts who administered their drugs intravenously. The initial complaints were those of generalized symptoms of infection. Of the physical signs, the most prominent were skin manifestations and especially petechiae. Joint involvement was present in one-third of the cases. Splenomegaly and meningismus were less common, as were subcutaneous abscesses; clubbing was not a feature. Proteinuria and microscopic hematuria were present in most cases.

Treatment with penicillin alone or with other antibiotics resulted in a mortality of about 50 per cent. The authors suggest that treatment be instituted as early as possible. The disease should be suspected on clinical grounds (cardiac murmurs, fever, and the presence of infections of the skin, bones, joints or meninges) and treatment begun after drawing blood for cultures at hourly intervals, even before bacteriologic study is completed.

Penicillin in doses of 1,000,000 units intramuscularly at two-hour intervals should be started at once. When penicillin sensitivity studies of the offending organism can be made, the dosage should be adjusted to produce a blood level of at least four times the minimal inhibitory concentration. Therapy should continue for four to six weeks.

ENSELBERG

Thomas, A. M.: Acute Infective Endocarditis Caused by Salmonella Dublin. Arch. Path. **53:** 408 (May), 1952.

The author records a case of acute endocarditis due to *Salmonella dublin*, involving the aortic valve, in a 53 year old woman. The patient had a prolonged fever of the enteric type, a positive blood culture unaltered by penicillin and sulfathiazole, a normal leukocyte count and normal heart sounds. The patient died on the twenty-eighth day of her illness. Autopsy revealed exuberant vegetations on the aortic valve superimposed on normal leaflets. The Salmonella was recovered from the heart vegetations. The writer emphasizes the high mortality of Salmonella endocarditis and questions the validity of one of the early case reports (Gouley and Israel) on the basis of the clinical recovery.

GOULEY

Flanders, J. F., McGee, L. C., and Scott, E. G.: Enterococcal Endocarditis: Report of a Case Treated with Aureomycin. Ann. Int. Med. **36:** 1323 (May), 1952.

Several months following the subsidence of an acute monarticular arthritis, a 34 year old negro male developed cough, chest pains, fever, vomiting, and hemoptysis. The physical examination revealed the presence of systolic and diastolic murmurs of the heart and evidences of a pneumonia. Blood cultures revealed the presence of *Streptococcus liquefaciens*. Sensitization studies indicated that this organism was resistant to penicillin, streptomycin and chloromycetin but was somewhat sensitive to Aureomycin. For this reason, intensive treatment with Aureomycin administered orally as well as intravenously was instituted. However, in spite of this treatment, the patient succumbed. The autopsy findings confirmed the diagnosis of bacterial endocarditis complicated by myocarditis and cardiac dilatation, congestion of the lungs and of the liver, infarction of the spleen, and infarction of the kidneys. At the time of death, blood removed from the arteries was sterile. It is therefore concluded that this case represents an instance of bacteriologic cure with a subsequent fatal outcome, and also represents an instance of enterococcal endocarditis due to *Streptococcus liquefaciens*, in which the offending organism was resistant to all antibiotics except Aureomycin, and apparently the infection was arrested by the drug. Death apparently resulted from the myocardial complications from the bacterial infection.

WENDKOS

BLOOD COAGULATION

Anfinsen, C. B., Boyle, E., and Brown, R. K.: The Role of Heparin in Lipoprotein Metabolism. Science **115:** 583 (May 30), 1952.

Since the administration of heparin caused a reorientation in the distribution of low-density lipoproteins and retarded the formation of high levels of S_f 10–50 lipoproteins, which may be in some way related to atheroma formation, the authors studied the heparin effect in an in vitro system. From other experiments, it appears that heparin administration activates or stimulates the production of a "clearing factor," which has the property of decreasing the turbidity of alimentary lipemic plasma. Perfusion experiments reveal that heart and lung tissues were most active in converting a plasma material into the clearing factor in the presence of heparin. Each of the components—tissue extract, heparin, and plasma—must be present for the production of active material, although a small but demonstrable formation of clearing factor was observed in certain plasma samples incubated with heparin in the absence of tissue factor; this suggests that tissue factor may occasionally exist in plasma in low concentrations.

The details of the fractionation studies are described. Most of the work was based on assays by the turbidity decrease method. However, ultracentrifugal tests on lipoprotein preparations before and after treatment with purified clearing factor indicate that lower S_f lipoproteins accumulated at the expense of higher S_f components. Further work is being done in the purification of the components of the clearing system and in a more detailed study of the mechanism of lipid labilization both in vivo and in vitro under the influence of these purified materials.

WAIFE

Cloetens, W., Tenzer, C., and Mascart, P.: Treatment with Anticoagulants in Thromboembolic Diseases. Acta Cardiol. **7:** 407 (Fasc. 4), 1952.

The authors report their experience in the treatment of 104 thromboembolic cases with Tromexan and a similar compound (Pelentan). The material included patients with phlebitis, with or without emboli, myocardial infarction, progressive coronary disease and auricular fibrillation with peripheral emboli. The therapeutic doses were adapted to maintain prothrombin levels in the blood at 10 to 30 per cent of normal, and prophylactic protracted doses were used to keep the level at 25 to 50 per cent of normal.

The results are classified as excellent especially

in cases with progressive coronary disease. Some instances were treated over prolonged periods, even more than two years, without serious accidents. Numerous cases were treated at home or during ambulation. The authors arrived at the conclusion that, with careful selection of patients and maintenance of proper dosage and of strict technics of blood controls, the dangers of the treatment are very small and complications minor and of no clinical importance.

PICK

Hagen, P.: The Effect of Hyaluronidase on the Absorption of Heparin. Med. J. Australia **1:** 471 (April), 1952.

Hyaluronidase increases the rate and degree of absorption of subcutaneously or intramuscularly injected heparin. Its effect is greater if some of the hyaluronidase is injected separately at the site before the injection of the heparin. The inhibition of hyaluronidase activity by heparin has been confirmed. Hyaluronidase does not inactivate heparin. Antihistaminics may inhibit hyaluronidase activity in proper dosage.

BERNSTEIN

CONGENITAL ANOMALIES

Healey, J. E., Jr.: An Anatomic Survey of Anomalous Pulmonary Veins: Their Clinical Significance. J. Thoracic Surg. **23:** 433 (May), 1952.

After reviewing the cases of anomalous pulmonary veins reported in the literature, the author presented three new ones. In two instances a left pulmonary vein received tributaries from all segments of the left upper lobe and then entered the left innominate vein. The left inferior pulmonary vein drained the left lower lobe and emptied normally into the left auricle. In the last case the left upper lobe was drained by a left superior pulmonary vein which was joined by the left superior intercostal vein and by an anomalous vessel. The combined trunk then entered the left innominate vein.

The author pointed out that anomalous pulmonary-systemic connections have clinical significance, and in the near future they may even be detected, using such diagnostic aids as cardiac catheterization and angiocardiography.

ABRAMSON

Souliè, P., Joly, F., Carlotti, J., Sicot, J. R., and Voci, G.: Pathophysiologic Postoperative Study in the Trilogy of Fallot (Study of Nine Cases Following Pulmonary Valvulotomy). Arch. mal. coeur **45:** 385 (May), 1952.

The authors report clinical, radiologic, electrocardiographic and catheterization studies in nine cases of Fallot's trilogy (pulmonic stenosis with interauricular communication), performed one month and nine months following valvulotomy. Although cyanosis remained more or less unchanged, a definite improvement of functional capacity was noted, beginning two to five months following surgery. None of the cases showed a diminution of heart size. Electrocardiographic changes were found only exceptionally and consisted in regression of anomalies of the P wave and in one instance, in diminution of the size of previously large QRS complexes, characteristic for heart strain. Right ventricular pressure decreased in cases with preoperative values over 150 mm. Hg, but in only two cases the pressure became lower than the pressure in the left ventricle. Pressure elevation in the pulmonary artery and increase of pulmonary flow never exceeded normal values. The direction of the interauricular shunt remained predominantly from right to left.

In the whole the results of the operation were very variable, and amelioration of the condition was seen to develop slowly and only to a limited degree. This may be due to the fact that certain parts of the congenital anomaly, like thickening of the infundibular portion of the right ventricle, are not changed by simple valvulotomy. However, observation over much longer time may be necessary to evaluate completely the results of the operation.

PICK

Jonsson, G., and Saltzman, G. F.: Infundibulum of the Patent Ductus Arteriosus Studied by Thoracic Aortography. Acta radiol. **37:** 445 (May), 1952.

The authors discuss their findings in 27 cases of patent ductus arteriosus subjected to thoracic aortography. In 25 of these there was an anterior bulge of the aortic wall, at the site where the ductus leaves the aorta. This site (infundibulum) is usually visible in both the postero-anterior and left anterior oblique positions. In two cases there was uniform widening of the upper part of the descending aorta. In the others the shape of the infundibulum varied from a shallow bulge up to a funnel-shaped formation.

A small bulge of the wall of the normal aorta was observed in a few cases; it never projected more than about 1 mm. and was visible only in the lateral views.

SCHWEDEL

Bret, J.: Indications and Results of Operations According to Blalock, Potts and Brock in 200 Cases of Pulmonary Stenosis. Arch. mal. coeur **45:** 577 (July), 1952.

The author presents his experience with various types of surgery in 150 cases of typical tetralogy and 50 cases of other cyanotic malformations including instances of pulmonary atresia with pseudotruncus aorticus, trilogy of Fallot and tricuspid atresia. A side-to-side anastomosis of the descending

aorta and left pulmonary artery is, in his opinion, the operation of choice in Fallot's tetralogy and in pseudotruncus communis. This type of approach is also indicated in congenital stenosis or atresia of the tricuspid valve. If unexpected and unsurmountable technical difficulties are encountered at surgery, an end-to-side, or end-to-end anastomosis of the left subclavian and pulmonary artery can be performed instead. The latter type of operation is primarily indicated in the presence of a right aortic arch. If, in the tetralogy, any type of anastomosis is impossible it is advisable to enlarge the incision to the right and to perform pulmonary valvulotomy or infundibular resection according to Brock. The latter are the only operations indicated in pulmonary stenosis with auricular septal defect (Fallot's trilogy).

PICK

Lubert, M., Epstein, H. C., Mendelsohn, H., and Freedlander, S. O.: An Unusual Variant of Double Aortic Arch. Am. J. Roentgenol. **67:** 763 (May), 1952.

These authors describe the clinical and roentgenographic findings in an infant with a double aortic arch. The main left aorta coursed to the left then behind the esophagus to descend to the right of the vertebral column; the smaller right arch coursed over the right bronchus from the ascending to the descending portions. Two indentations were present in the barium esophagram in the postero-anterior position, one on the left side, another on the lower right side. This type of aortic anomaly must be differentiated from instances of double aortic arch with the right larger and with a left descending aorta, from a left aortic arch with a right descending aorta and from a right aortic arch with right descending aorta with anterior esophageal displacement from the left ligamentum arteriosum.

SCHWEDEL

Russell, K. P., Dallke, W. E., and Buell, J. I.: Pregnancy Following Blalock Operation for Tetralogy of Fallot. J. A. M. A. **149:** 266 (May 17), 1952.

A case of pregnancy following the Blalock operation for tetralogy of Fallot is reported. After cardiac surgery, the patient, who previously would have been considered a grave obstetric risk, was successfully carried through pregnancy. Under caudal anesthesia, vaginal delivery was effected with moderate calculated maternal and fetal risk. While no conclusions can be drawn from one case, the report suggests that pregnancy may not be permanently contraindicated in poor risk patients with cardiac lesions amenable to surgery.

KITCHELL

CONGESTIVE HEART FAILURE

Thoresch, P. A., Baldwin, A. D., Morris, C. M., and Leikel, W. J.: Planning Low-Sodium Meals: A Community Project. New England J. Med. **246:** 771 (May), 1952.

This report concerns a study of low-sodium diets undertaken in Newton, Mass., as an activity of the joint Heart Demonstration Program of the Newton Health Department and the United States Public Health Service. After a preliminary study disclosed some of the inadequacies of the usual low-sodium diet instruction material, a nutritionist visited 41 patients referred by their physicians for individual instruction in their homes. In many instances instructions had been incomplete or not practical enough; many patients did not appreciate that the diet could be prepared with regular family meals; teaching the use of a variety of sodium-free seasonings was needed to relieve the "flat" taste of the diet. A need for standardization of the diet instructions was soon appreciated. The degree of sodium restriction which had been ordered was found to vary from unnecessarily severe to ineffectively mild. Caloric levels were prescribed very precisely at times and at other times were disregarded. Based on this experience the Nutrition Subcommittee developed standardized nutritionally adequate low-sodium diets. Diets were prepared for patients on three sodium levels, 200, 400, and 800 mg. of sodium, and for each of three caloric levels, 1200, 1500, and 2000 calories. To make the diet information available to patients in an easily understood form, a booklet on planning low-sodium meals was prepared. The booklet was intended to show that a restricted sodium diet can be appetizing and nutritious. It was written in simple language and illustrated. The booklet was given to patients only on a physician's order. The acceptance of this standardized diet material by physicians and patients is said to have led to a nearly uniform approach to low-sodium diet education throughout the community. Individual and group diet-education services for patients on low-sodium diets are said to have been another outgrowth of this project.

ROSENBAUM

Barger, A. C., Roe, B. B., and Richardson, G. S.: Relation of Valvular Lesions and of Exercise to Auricular Pressure, Work Tolerance, and to Development of Chronic, Congestive Failure in Dogs. Am. J. Physiol. **169:** 384 (May), 1952.

The present study was undertaken to investigate the relation of valvular lesions and of exercise to auricular pressure, exercise tolerance and the development of congestive failure in the unanesthetized dog. Pulmonary regurgitation of long standing had little if any effect on auricular pressure or work tolerance. Pulmonary stenosis, alone or combined with insufficiency, produced an elevation of central venous pressure during exercise even though there was little or no elevation of auricular pressure at rest. There was normal tolerance to exercise in these cases. Although tricuspid regurgitation gave

an elevated auricular pressure at rest with further increase during exercise, work capacity was normal. When pulmonary stenosis and tricuspid insufficiency were combined the resulting findings resembled right-sided congestive failure in man.

OPPENHEIMER

Albert, R. E., and Eichna, L. W.: The Response of the Peripheral Venous Pressure to Exercise in Congestive Heart Failure. Am. Heart J. **43:** 395 (March), 1952.

The authors have studied the venous pressure at rest and during exercise in 27 patients with varying degrees of congestive heart failure, in 12 patients with pulmonary disease, and in 20 patients without cardiac or pulmonary disease.

Exercise consisted of flexing one leg completely 30 times a minute for two minutes. The venous pressure of patients with pulmonary disease was lower than that of the control group possibly due to an error in the positioning of the zero reference level in the former. However, there was no significant difference in the rise in venous pressure during exercise in the two groups, 26 and 21 mm. of water, respectively. In general, both the resting venous pressure and the rise in venous pressure during exercise increased with the severity of the congestive heart failure. Serial determinations were made on six patients as they recovered from severe congestive heart failure and showed a progressive decrease in the resting venous pressure and a smaller rise in venous pressure during exercise.

The venous pressure response to exercise is a more sensitive index of the milder degrees of congestive heart failure than the venous pressure at rest, since 50 per cent of the determinations at rest and 73 per cent during exercise were abnormally increased. Since most patients with severe failure had abnormally high venous pressures at rest, the venous pressure response to exercise was of little further value.

HELLERSTEIN

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Gofman, J. W.: Diet and Lipotrophic Agents in Atherosclerosis. Bull. New York Acad. Med. **28:** 279 (May), 1952.

The lipoproteins in human serum may be characterized by their flotation rate in a salt solution by the analytic ultracentrifuge. This is described in terms of Svedberg units (S_f units). Human serums differ from one another in the number of types of lipoproteins present and in the relative concentration of each of the various species. Studies of lipoprotein patterns have shown a high quantitative association of the S_f12-20 and S_f20-100 classes with atherosclerosis. This is independent of the total serum cholesterol level. A definite correlation between obesity and S_f12-100 lipoprotein level was found. This association may account for the increased incidence of atherosclerosis in obese individuals. With calorie restriction and weight loss, and also with a low fat intake, a reduction of elevated S_f12-100 lipoprotein levels was found. This varied considerably from one individual to another and was not universally effective. The authors, however, believe that this reduction occurs often and frequently enough to warrant the trial of a low-fat diet plus obesity correction as an approach in the management of atherosclerosis. Heparin has been found to be a pharmacologic agent which may shift lipoprotein patterns towards the normal human distribution with a marked reduction of elevated S_f12-100 classes. The effect of long term heparin administration for the purpose of lipoprotein alteration is not known as yet. The action of heparin suggests the possibility of lipoprotein control through pharmacologic means.

SAGALL

Thannhauser, S. J.: The Significance of Cholesterol in the Pathogenesis of Vascular Lesions. A Discussion of the Intracellular Accumulation of Cholesterol in the Intima and of the Extracellular Precipitation of Cholesterol in the Arterial Tissue. New England J. Med. **246:** 695 (May 1), 1952.

It is emphasized that since the organism is able to synthesize cholesterol from metabolites of low-carbon chains, especially from acetic acid, it is evident that synthesis of cholesterol cannot be prevented by the restriction of any kind of foodstuffs. In any consideration of sterol metabolism the cycle of excretion and reabsorption of cholesterol and its intestinal bacterial-degradation products must be borne in mind. Cholesterol is said to accumulate in the arterial tissues by two processes: (1) intracellular accumulation of cholesterol in the intimal and subintimal cells, as in familial and experimental hypercholesterolemia, in which excess accumulation of cholesterol in the serum is the primary cause, and (2) extracellular precipitation and crystallization of cholesterol in a primarily altered arterial tissue, in which the alteration and damage in the arterial wall, arising in several ways, is the primary lesion and cholesterol deposition is only secondary; this second process is believed to characterize the more common type of arteriosclerosis. Calcium deposition and cholesterol precipitation in the altered arterial wall are felt to be probably analogous physicochemical processes secondary to the structural and physical changes of the tissue. A diet low in cholesterol and neutral fats is recommended in familial hypercholesteremia as well as in conditions associated with hyperlipemia. In the treatment of the common type of arteriosclerosis of the higher-age group, a diet low in calories, irrespective of its cholesterol content, is considered to be sufficient.

ROSENBAUM

McGill, R. J.: Cardiac Contusion—Differentiation from Cardiac Infarction. Lancet **6716:** 997 (May), 1952.

Apart from a history of injury, the clinical features of cardiac contusion and cardiac infarction may be very similar. In cardiac injury there may be no obvious bruising of the chest wall or fracture of the bones of the thorax, this being especially true in the elastic chest of the young. Preceding malaise or mild discomfort in the chest are features, if obtainable, peculiar only to infarction. If the lesion occurs during violent exertion, contusion is the more likely diagnosis. Clinically, in contusion and in infarction, there may be the same collapse, with pallor and sweating, desire to pass urine and defecate, low blood-pressure, tachycardia, faint heart sounds, and similar electrocardiograms.

The difficulty in differentiating histologically between the results of coronary occlusion and trauma of the heart muscle is well exemplified in this case and is of considerable medicolegal interest.

BERNSTEIN

Schimert, G., Blomer, H., and Schimler, W.: Studies on Cardiac Dynamics in Experimental Coronary Occlusion; a Contribution to the Clinical Significance of the Bezold-Jarisch Reflex. Ztschr. Kreislaufforsch. **41:** 337 (May), 1952.

Blood pressure, pulse wave velocity, stroke volume and several other circulatory values which can be determined with the help of the formulas of Broemser and Ranke, were recorded in 12 dogs, before and following ligation of one the main coronary arteries. In the majority of experiments the following acute changes in the circulation were observed: cardiac output and stroke volume decreased in the average by about 50 per cent, and the peripheral resistance increased; mean blood pressure and the pulse pressure fell; variations of the heart rate occurred but were inconstant.

These changes are explained by the authors from a teleologic viewpoint. Circulatory collapse subsequent to myocardial infarction is not due to circulatory failure but appears to represent a reflex adaptation of the organism in order to maintain circulation on a lower level. The reflex character of this adaptation is apparent from the fact that the vasomotor reactions can be prevented or abolished by cooling the vagi. This reflex is similar to that described by Bezold and Jarisch and its purpose is to diminish cardiac output. This is effected mainly by reduction of the venous return to the heart and probably also by inhibition of the sympathetic tone in the heart. The reflex seems to be initiated by humoral factors (accumulation of metabolic products in the area of infarction and/or mechanical loss of contractility of a circumscribed area of the myocardium).

PICK

Adlersberg, D., and Zak, F. G.: Coronary Atherosclerosis in the Young: Clinical and Pathological Observations. J. Mt. Sinai Hosp. **19:** 289 (May–June), 1952.

A comparative study was made of a young group (ages 27 to 46) and an old group (ages 60 to 83), comprised of 50 persons each, with fatal coronary artery disease. The younger group is characterized by an increased familial occurrence of heart disease, a shorter clinical history and shorter average duration of anginal pain and cardiac failure, a greater preponderance of men, a greater preponderance of overweight women, a high incidence of heavy smokers, a significantly lower incidence of hypertension and diabetes (one-fourth to one-third of that found in the older group), and higher levels of serum cholesterol (average, 348 as against 275 mg. per 100 ml.).

The pathologic studies revealed that the younger group showed a greater incidence of extreme heart weights (500 Gm. and more) despite the higher incidence of hypertension in the older age group. The differences between the two age groups in the microscopic structure of the coronary arteries were less clear cut, although the younger group had a greater tendency to fibrous intimal proliferation, while the older patients had more atheroma and calcification. The youngest patient of the group, a man of 27, revealed a segmented coronary artery lesion with the features of the acute phase of "arteriitis stenosans coronariae." Only mild atherosclerosis was found in the remainder of the coronary tree and only moderate sclerosis of the aorta was observed.

CORTELL

Scott, R. C., and Seiwert, V. J.: The Treatment of Angina Pectoris with Pure Crystalline Khellin. Ann. Int. Med. **36:** 1190 (May), 1952.

Fourteen patients with well-authenticated angina pectoris were treated with an oral preparation of pure crystalline khellin (Khelloyd). Classifying the cases on the basis of the severity of their angina during the control period, three had mild angina (fewer than two pains per week), seven had moderate angina (between two and 10 pains per week), and four had severe angina (over 10 pains per week). Each patient was given either 50 mg. doses of crystalline khellin four times a day, or a placebo identical in size and color. This trial with either khellin or placebo was conducted for an average of four weeks. At the end of this period the preparations were changed, and those who had been receiving placebo were now given khellin, and vice versa. The physician who dispensed the tablets did not know their identity. Eight of the 14 patients experienced fewer pains while taking the purified crystalline khellin than during either the control period or while taking placebo. Five of these patients had

over 50 per cent reduction in the frequency of their anginal attacks. Three of the four severe cases, four of the seven moderate cases, and one of the three mild cases showed significant improvement while taking the drug. Six of the patients showed no significant decrease in the frequency of their pains while taking purified crystalline khellin. The most common side effect observed was the appearance of nausea, but this symptom was readily controlled in most cases by reduction of dosage. All except one of the 14 patients were maintained on an average daily dose of purified crystalline khellin of 100 mg. or more throughout their period of treatment. By contrast, a khellin mixture in the same dosage generally could not be employed because of untoward effects. Some patients receiving daily doses ranging between 100 and 200 mg. of purified crystalline khellin did not benefit from the drug, indicating that the drug cannot be expected to be of help in every patient with coronary disease.

WENDKOS

ELECTROCARDIOGRAPHY

Feldman, E., Wosika, P. H., Chesrow, E. S., and Pipilis, G. A.: A Comparison of Precordial Electrocardiograms using Indifferent Electrodes V, CR, and RS. Am. J. M. Sc. **223:** 522 (May), 1952.

Supine electrocardiograms were obtained on 98 subjects using standard leads, augmented unipolar limb leads, precordial leads V_1–V_7, CR_1–CR_7, and RS_1–RS_7. The purpose of this study was to compare the indifferent precordial electrodes V, CR, and RS to determine whether significant differences existed between the curves depending upon the type of electrode employed. The authors found that the P, QRS, and T deflections from the right precordium tended to be more positive in the CR and RS leads. These variations were attributed to the right arm potential as seen in aV_R. Thus, the predominating negative P wave in aV_R was associated with an upright P wave in CR and RS leads. The CR and RS leads are similar in configuration indicating that the right scapula is not indifferent but has a potential similar to the right arm. The influence of this potential may be sufficient to obscure the diagnosis of anteroseptal infarction or of right ventricular hypertrophy as demonstrated by exemplary cases. It is suggested that the central terminal be used routinely for electrocardiographic work.

SHUMAN

Van Dooren, F., and Boyadjian, N.: Electrocardiographic and Clinical Study of the Syndrome $T_1 < T_3$. Acta cardiol. **7:** 301 (Fasc. 3), 1952.

Among 3000 electrocardiograms 100 were found revealing the pattern of T_1 smaller than T_3. The cases were analyzed according to clinical findings and other associated electrocardiographic anomalies. The clinical diagnosis was coronary insufficiency in 27, angina pectoris in 22, pulmonary disease without cardiac involvement in 18, a pendulous normal heart in 20, mitral disease in five and right bundle branch block in seven.

According to the authors the pattern $T_1 < T_3$ suggests coronary disease if it is found in an elderly person with hypertension and an enlarged heart, and is associated with left axis shift and an electrically horizontal position and with inverted or flattened T waves in precordial leads. It suggests, on the other hand, a positional change of a normal heart when it is present in a younger individual with a roentgenologically vertical heart, and is associated with right axis shift and a deep S wave in lead I and V_6. Myocardial infarction revealing this pattern rarely shows alterations of the QRS complex, has a good prognosis and is localized at the basal portions of the left ventricle.

It is concluded that the outlined clinical and electrocardiographic criteria are in the majority of cases sufficient to establish the cause of the $T_1 < T_3$ pattern.

PICK

Essen, K. W., and Siefert, H.: What Is the Value of the Ergotamine Test in the Differential Diagnosis of Functional and Organic Alterations of the Electrocardiogram? Ztschr. Kreislaufforsch. **41:** 430 (June), 1952.

The authors studied the effect of a single intramuscular injection of Hydrergine upon various types of electrocardiographic anomalies present in resting tracings of 55 patients.

The cases were divided into etiologic groups. In one group consisting of cases with neurocirculatory asthenia, the electrocardiogram became normal following the injection in all instances. In six patients with valvular lesions and in six with myocarditis, the abnormal tracing did not change. The same was true in 23 instances with coronary disease. In two cases with severe neurosis, cardiac complaints and abnormal electrocardiograms, Hydrergine remained likewise without effect.

Although restitution of an abnormal electrocardiogram to normal following administration of Hydrergine suggests a functional anomaly, an associated organic lesion can never be completely ruled out. On the other hand, the disturbance of the vegetative nervous tone can, in some persons, reach such a degree that the resulting electrocardiographic anomalies become irreversible. Prognostic conclusions based upon the result of the Ergotamine test require, therefore, caution and should not be made without a total examination of the patient.

PICK

DeCossio, A. G.: Electrocardiographic Changes Under Emetine Therapy. Am. Heart J. **43:** 456 (March), 1952.

The author studied a group of 45 patients with amebiasis (and no heart disease), undergoing treatment with intramuscular emetine. The most noteworthy electrocardiographic change was the inversion of the T wave in the precordial leads (seven days after onset of emetine therapy), since it was the first change to appear, occurred in 100 per cent of the cases, and disappeared on an average of 53 days after the end of therapy. Prolongation of Q-T occurred in 90 per cent and disappeared 50 days after end of therapy. In the standard limb leads T-wave changes occurred in 18 per cent of the cases. The ventricular gradient did not show significant changes. One patient died of an overdose of emetine (total dose 1.50 Gm.). Microscopic sections of the myocardium showed myocardial degeneration.

The author emphasizes the hazard of emetine treatment in patients with coronary disease since a toxic drug action may be added to previously damaged myocardial fibers.

HELLERSTEIN

Lian, Cassematis, and Hebert: The Value of the Auricular Precordial Lead S_5 in the Diagnosis of Disorders of Auricular Rhythm. Arch. mal. coeur **45:** 481 (June), 1952.

Various technics of recording auricular potentials over the precordium were tried in cases with abnormalities of auricular activation. The best results in recording auricular activity, not or hardly visible in conventional leads, were obtained when, using lead I, the right arm electrode was placed over the manubrium of the sternum, and the left arm electrode was placed parasternal in the fifth intercostal space. With the help of this technic various types of auricular arrhythmias could be readily differentiated. The described bipolar lead, termed S_5, is, according to the authors, mainly influenced by proximity potentials originating in the auricles and cannot be explained on a vectorial basis.

PICK

Segers, M., Pannier, R., Van Loo, A., and Van Beylen, C.: Repercussion by Distance of Auricular Activity in Electrokymographic Tracings. Acta cardiol. **7:** 399 (4), 1952.

The authors present electrokymograms obtained from various points of the cardiovascular shadow, distant from auricular structures, which show definite evidence of auricular activity. This was found in cases of complete and partial A-V block, where a small upright wave was recorded in various portions of the cardiac cycle and always in a fixed time relationship to the P wave in a simultaneously recorded electrocardiogram. Similarly, small waves reflecting auricular activity could be demonstrated during normal rhythm. Here, the auricular wave shortly preceded, or was partly superimposed upon, curves obtained from the right or left ventricular borders, from the level of the pulmonary artery, and was especially distinct at the right border of the ascending aorta. In the latter location it can deform the tracing to such a degree that its interpretation and particularly the timing of onset of ventricular ejection may become inaccurate. In view of these observations the authors recommend that aortic electrokymograms be recorded from the left border of the aorta.

PICK

Lepeschkin, E.: Distortion of Electrocardiographic Effects of Intravenously Injected Solutions Due to Cooling of Myocardium. Am. J. Physiol. **169:** 400 (May), 1952.

When more than 2 ml. of an aqueous solution (Ringer solution) at room temperature is injected rapidly by vein into experimental animals there is a transient change in T wave and heart rate. Duration of these changes is less than 11 seconds after the end of the injection. Cooling of the myocardium is responsible for these effects. Injected solutions should be at a temperature 1 C. less than rectal temperature.

OPPENHEIMER

Langendorf, R., Lev, M., and Pick, R.: Auricular Fibrillation with Anomalous A-V Excitation (W-P-W Syndrome) Imitating Ventricular Paroxysmal Tachycardia. A Case Report with Clinical and Autopsy Findings and a Critical Review of the Literature. Acta cardiol. **7:** 241 (Fasc. 3), 1952.

Clinical, electrocardiographic and autopsy data are reported in a case of rheumatic heart disease associated with the syndrome of Wolff-Parkinson-White and auricular fibrillation and flutter. Histologic studies of the auriculoventricular junction, although incomplete, permitted the exclusion of muscular connections of the right auricle and the A-V node to the right ventricle, of the type described by Kent and by Sanabria; however, a connection to the left ventricle could not be ruled out.

During auricular fibrillation there were two types of ventricular complexes, the first indicating right heart strain, the other similar to the Wolff-Parkinson-White type seen during sinus rhythm. The latter disappeared on quinidine medication, and reappeared following digitalis therapy, which in turn failed to depress the ventricular rate. When both types of ventricular complexes were present, the wide ones showed tendency to a particular grouping, simulating ventricular premature beats of ectopic origin and ventricular paroxysmal tachycardia. Transition between normal and anomalous beats occurred over beats of intermediate contour.

On the basis of the analysis of the presented material and a critical review of the literature, the authors conclude that the majority of instances so far reported to represent ventricular paroxysmal tachycardia associated with the Wolff-Parkinson-

White syndrome were actually instances of paroxysmal auricular fibrillation with prevalent anomalous A-V conduction through the accessory pathway. This, on the other hand, excludes other theories offered to explain the mechanism of the Wolff-Parkinson-White syndrome, especially the assumption of a hyperexcitable ventricular focus. However, the cause of the not infrequent association of the Wolff-Parkinson-White syndrome with auricular fibrillation or flutter remains obscure.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Robson, H. N., and Duthie, J. J. R.: Further Observations on Capillary Resistance and Adrenocortical Activity. Brit. M. J. **4776:** 994 (May), 1952.

Cases of hypopituitarism were found to have abnormally low capillary resistance. These patients did not respond to single injections of 25 mg. of adrenocorticotropic hormone, but when repeated doses of the hormone were given a rise in resistance was obtained. Distinct rises in resistance followed the administration of cortisone, either intramuscularly or orally.

Desoxycorticosterone acetate caused a fall in resistance, while progesterone, testosterone, estradiol, and pregnenolone were without effect. Rises in capillary resistance which follow nonspecific stress are due to increased adrenocortical activity and increased output of glucocorticoid hormone. The test has been found to be a simple and sensitive index of adrenocortical response to stimuli.

BERNSTEIN

Sussman, N.: The Use of Cortisone in the Management of the Shoulder-Hand Syndrome. Arch. Physical Med. **33:** 289, (May), 1952.

Although the shoulder-hand syndrome is initiated by many different causes, the under-lying neurovascular mechanism is probably the same. It is the opinion of most that this phenomenon is initiated from an area of local tissue disturbance such as a traumatized extremity, a myocardial infarct or an area of cerebral pathology, any site of external or internal disturbance to tissue.

Although the mechanism by which cortisone acts is still open to conjecture, its therapeutic effectiveness has been demonstrated in an ever-increasing spectrum of disease entities. As is illustrated by the case reported here, this steroid is recommended in the management of the shoulder-hand syndrome for the following reasons: (1) its analgesic effect, (2) resultant increased sense of well-being, (3) increased amenability to adjunctive physiotherapy, (4) progressive reversal of the existing pathologic state.

BERNSTEIN

HYPERTENSION

Evans, B., and Enderby, G. E. H.: Controlled Hypotension and its Effect on Renal Function. Lancet **1:** 1045 (May), 1952.

Fifty patients receiving hexamethonium bromide during anesthesia were compared with 50 not receiving the drug, special reference being made to proteinuria and fluid excretion. Although proteinuria with or without casts and red cells was commoner in the hexamethonium series, the difference is of doubtful or negative statistical significance.

The conclusion may be drawn that if renal function is normal before operation, it is unlikely to be appreciably impaired by hypotension induced for surgical purposes with hexamethonium bromide.

BERNSTEIN

Moser, M., Walters, M., Master, A. M., Taymor, R. C., and Metraux, J.: Chemical Blockade of the Sympathetic Nervous System in Essential Hypertension. Arch. Int. Med. **89:** 708 (May), 1952.

An adrenergic blockade was established and maintained by oral medication with a new sympathetic blocking agent, 688-A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride), in 11 patients with essential hypertension. Blockade was irregular when enteric-coated tablets were used but was continuous when gelatin capsules were substituted. Dosage varied from 1 to 4 mg. per kilogram of body weight per day and was less with the latter preparation.

A significant fall in recumbent diastolic pressure was obtained in 5 of the 11 patients. Significant lowering of diastolic blood pressure in the upright position occurred in 9 of the 11 patients. Recumbent and postural effects on the blood pressure and the cold-pressor response in hypertensive patients seem to compare favorably with results obtained in patients subjected to surgical sympathectomy.

Severe toxic reactions did not occur, but side-effects such as weakness, drowsiness, nasal stuffiness, and palpitations, proved annoying in several patients. It is suggested that therapy with 688-A be carried out on large groups of patients to determine whether its long-term effects on hypertensive patients will compare favorably with results of surgical treatment and whether this drug has a place in the therapy of essential hypertension.

BERNSTEIN

Mackinnon, J.: Effect of Hypotension-producing Drugs on the Renal Circulation. Lancet **2:** 12 (July 5), 1952.

The effect of pentamethonium iodide on the renal circulation has been investigated. The glomerular filtration-rate and effective renal blood-flow are reduced by this drug. The effective renal blood-flow is reduced even when the fall in blood-pressure is

small, and the reduction is greater than can be accounted for solely by a lowering of the blood-pressure. Renal resistance is increased, owing to renal vasoconstriction. In hypertensive patients the effective renal blood-flow is increased by administration of prep. 5968, and the blood-pressure is reduced. Change in glomerular filtration rate is inconstant, and renal resistance is diminished.

BERNSTEIN

Swiss, E. D., and Maison, G. L.: The Site of Cardiovascular Action of Veratrum Derivatives. J. Pharmacol. & Exper. Therap. **105:** 87 (May), 1952.

The actions of Veriloid, Protoveratrine, Veratridine and Veratramine were studied by cross circulation experiments in dogs which could separate the actions of these alkaloids when confined to the head or body circulation. Bradycardia was not produced when these drugs were isolated in the head circulation, but a fall in blood pressure did occur. This hypotensive response was not abolished by atropine or vagotomy. The production of bradycardia from all four agents required that the drug reach the body circulation. The hypotensive action of Veriloid and Protoveratrine after injection into the body circulation depended on slowing of the heart and could be eliminated by atropine. Slight bradycardia and hypotension still appeared after atropine after the administration of Veratridine or Veratramine. The convulsive action of Veratramine was found to be a central action. The authors believe on the basis of their data that the central hypotensive effect of these alkaloids is probably more important clinically than hypotension following bradycardia produced by way of the vagus nerves.

SAGALL

Wilkins, R. W., Culbertson, J. W., and Rymut, A. E.: The Hepatic Blood Flow in Resting Hypertensive Patients before and after Splanchnicectomy. J. Clin. Investigation **31:** 529 (May), 1952.

Using the bromsulfalein extraction method for hepatic blood flow, the authors studied 41 hypertensive patients and 21 normotensive patients. The estimated hepatic blood flow was not significantly different and the calculated hepatic-portal resistance was significantly higher in hypertensive than in normotensive persons. Although shortly after splanchnicectomy the estimated hepatic blood flow is increased, the hepatic portal resistance decreased as compared with preoperative measurements. Within 4 to 10 months after the operation these values in hypertensive subjects return to their preoperative levels.

WAIFE

Blainey, J. D.: Hexamethonium Compounds in the Treatment of Hypertension. Lancet **6716:** 993 (May), 1952.

A trial, extending over six to nine months, of oral and subcutaneous hexamethonium compounds in 34 patients with severe hypertension is reported. The variation in blood-pressure was studied in detail before treatment so as to allow each patient to act as his own control. A considerable fall of blood-pressure took place in all the patients between the first consultation visit and the end of the control period of observation with rest in hospital alone. A slight further fall in the basal blood-pressure took place in some patients during the period of hexamethonium treatment in hospital.

Three months after discharge from hospital the blood-pressure had returned to pretreatment levels in all the patients, although there was considerable symptomatic improvement. The effect on the blood-pressure was similar with oral and subcutaneous administration, except that the latter in adequate dosage always produced a postural fall of blood-pressure on standing, often to below basal levels. This postural fall was of short duration and cannot be regarded as control of the hypertension, since it seems to be solely the result of interference with normal postural reflex circulatory mechanisms. Serious impairment of renal function directly due to hexamethonium was observed in three patients with malignant hypertension.

BERNSTEIN

Grimson, K. S., Orgain, E. S., Rowe, C. R., Jr., and Sieber, H. A.: Caution with Regard to Use of Hexamethonium and "Apresoline." J. A. M. A. **149:** 215 (May 17), 1952.

One hundred and three patients have been treated by the authors with hexamethonium chloride or bitartrate during the 18 months prior to the publication of the paper. Eight of these patients were treated with combined therapy using hexamethonium chloride or bitartrate in amounts up to 5 Gm. per day and an additional dose of hydrazinophthalazine in amounts varying from 50 mg. every other day in one patient to 50 mg. every two hours in another patient. There were numerous episodes of rather serious side effects most frequently involving episodes of prostrating hypotension, obstipation and ileus. The authors feel that the hydrazinophthalazine usually does not significantly lower the blood pressure beyond the level already accomplished by hexamethonium, but their series with combined therapy is not large enough to warrant definite evaluation at this time.

The main purpose of this report consists in the cautions in the use of these drugs. This includes slow institution of therapy during observation in a hospital; prerequisite initial examinations should be carefully made, including retinoscopic study to exclude papilledema with associated encephalopathy and hazard of respiratory arrest from sudden reduction of blood pressure. Such patients with encephalopathy or damaged myocardium should be given the drugs (if they are used at all) in very

small amounts with extreme caution. It is also noted that patients previously treated by sympathectomy tolerate much smaller doses and should receive very small initial doses. All patients on the drugs should be instructed concerning side effects and associated hazards; sedatives and salt depletion diets should be used carefully, and it should be realized that with either drug tolerance for alcohol may be decreased. Combined use of these drugs should be considered by all investigators as experimental procedures associated with definite hazards.

KITCHELL

PATHOLOGIC PHYSIOLOGY

Fourman, P.: The Ability of the Normal Kidney to Conserve Potassium. Lancet **1:** 1042 (May), 1952.

Potassium deficiency was studied in two normal persons to determine whether they could conserve potassium. A negative potassium balance was induced with a cation-exchange resin given for 12 days to one person and twice for 16 days to the other. Resin administration was accompanied by acidosis. The total potassium deficit amounted to about 700, 500, and 800 mEq. in the three experiments.

The urine-potassium level fell below the plasma-potassium level, showing that the kidney tubules can reabsorb potassium against a concentration gradient. Reabsorption was maximal during the recovery period, after the acidosis had been corrected. If patients with potassium deficiency continue to lose potassium, it may be because of adrenal overactivity, but not because of any inherent property of the kidney to waste potassium.

BERNSTEIN

Berger, E. Y., and Steele, J. M.: Suppression of Sodium Excretion by the Colon in Congestive Heart Failure and Cirrhosis of the Liver Demonstrated by the Use of Cation Exchange Resins. J. Clin. Investigation **31:** 451 (May), 1952.

There is increasing evidence that there exists a hormonal disturbance in certain disease states in which edema fluid accumulates. There is evidence that desoxycorticosterone diminishes excretion of sodium by the kidney, sweat glands, salivary glands, and colon. There is also evidence that the sweat and salivary glands in the patient accumulating edema act in a fashion resembling excessive desoxycorticosterone-like activity.

Patients with severe sodium retention (a daily urinary excretion negligible to the dietary intake of sodium) were studied. In order to insure sufficient amounts of sodium in the stool to permit quantification of a difference between normal and edematous subjects, a cation-exchange resin was used.

Under the conditions of this experiment it has been demonstrated that the colon of the edematous patient retains sodium to a greater degree than the colon of normal subjects. This suppression of sodium excretion is part of a generalized phenomenon involving the kidneys, sweat glands, and salivary glands. It appears that accumulation of edema in congestive heart failure, as well as in cirrhosis of the liver, is at least partly mediated through a disturbance in the endocrine regulation of sodium metabolism.

WAIFE

Kovacs, K., and Bachrach, D.: Hypothalamus and Water Metabolism. Studies on the Antidiuretic Substance of the Hypothalamus and Hypophysis. Acta med. scandinav. **141:** 137, 1951.

By means of biologic titration the antidiuretic activity of the hypophysis and hypothalamus of rats was studied by these observers. The extract of hypothalamus was found to possess antidiuretic activity although the hypophysis contains 20 times more antidiuretic substance than the hypothalamus of the same rat. In those reactions in which the antidiuretic hormone of the neurohypophysis is discharged into the organism, as in response to alarm, adrenalectomy or hypertonic saline administration, there is also a decrease in antidiuretic substance of the hypothalamus. These studies are said to suggest that alkaline phosphatase activity of the kidneys is not influenced by extracts of hypothalamus and that alkaline phosphatase plays no role in the mode of function of diuretic or antidiuretic drugs. Since the antidiuretic substance of the neurohypophyseal-hypothalamic system was found to show a quantitative decrease following the shock phase of the alarm reaction, this system is felt to play an active part in defense against nonspecific damage just as the anterior lobe of the pituitary does. These studies are said to indicate that the antidiuretic substance of the hypothalamus is released and takes part in the maintenance of the organism's equilibrium just as much as does that from the neurohypophysis. Therefore the antidiuretic substance of the hypothalamus may be considered a hormone depot which is mobile and is released in response to certain influences when the organism is in need of antidiuretic hormone to maintain equilibrium of water metabolism.

ROSENBAUM

Nelson, W. P., and Welt, L. G.: The Effects of Pitressin on Metabolism and Excretion of Water and Electrolytes in Normal Subjects and Patients with Cirrhosis and Ascites. J. Clin. Investigation **31:** 392 (April), 1952.

This study was designed to determine whether patients with cirrhosis and ascites are more sensitive to endogenous or exogenous antidiuretic hormone, and whether these patients were unable to inactivate or eliminate these substances normally. Eight normal subjects and seven patients with hepatic cirrhosis and ascites were studied. It was found that the normal subjects and the cirrhotics with ascites did not differ in the time required to achieve a maximal rate of diuresis in response to a water load, or in the

intensity or duration of the antidiuresis promoted by a dose of 2.5 or 100 milli-units of Pitressin.

WAIFE

Boucek, R. J., Grindlay, J. H., and Burchell, H. B.: Experimental Constrictive Pericarditis: Analysis of Induced Circulatory Failure. Am. J. Physiol. **169:** 434 (May), 1952.

Constrictive pericarditis was produced by Dakin's Solution. Most dogs had increased venous pressure, ascites and hind leg edema as a result of this technic. Renal function and blood were unchanged. There was no pulmonary edema. One animal had pulmonary edema, enlarged blood volume, small changes in venous pressure without ascites. The authors point out that resection of the constricting pericardium should include that portion of the pericardium over the left and right inflow tracts. The possible role of the escape of liver lymph into the peritoneal cavity in the production of ascites is discussed.

OPPENHEIMER

Frank, H. A., Cahan, A. M., and Banks, H.: Circulatory and Respiratory Effects of Continuous Versus Phasic Lung Inflation in Open-chest Dogs. J. Thoracic Surg. **23:** 465 (May), 1952.

The authors attempted to evaluate the degree of circulatory and respiratory disturbance produced by continuous lung inflation as conventionally employed during thoracic surgery. The study was performed on dogs under ether anesthesia, with the chest open and continuous inflation being carried out for periods of two hours or less.

It was found that cardiac output fell to a greater degree than might be expected on the basis of the intrapleural pressure change alone. The mean level of intrapulmonary pressure appeared to play a role in altering the readings. With regard to pulmonary changes, an adverse effect of continuously maintained positive respiratory pressure was a decline in ventilation. There was so little tidal exchange that the elimination of carbon dioxide was inadequate, resulting in severe respiratory acidosis.

Various attempts were made to counteract the acidosis. Allowing the lung to collapse completely and then refilling it with oxygen was not effective, nor did periodic, partial emptying and reinflating the lung at intervals prevent carbon dioxide accumulation. It was found that the adverse changes could be minimized or avoided by interrupting the positive respiratory pressure to permit passive exhalation against atmospheric pressure.

ABRAMSON

Bishop, H. F., Ciliberti, B. J., and Barendrick, E. H.: Venous Pressure During Surgical Anesthesia. A Preliminary Report. Anesthesia **13:** 297 (May), 1952.

Venous pressure determinations are an established aid in evaluating function of the right heart and pulmonary system, but there is little information in the literature concerning the effect of the operation and the anesthesia on the venous pressure The authors present an easy method for minute-to-minute measurement of the venous pressure during operations. They also present an outline of the clinical observation and studies that must be made in order to evaluate variations in venous pressure during surgical anesthesia so that these recordings may be employed as a valuable guide in the management of patients during surgery.

SAGALL

Carlotti, J., Joly, Fr., Sicot, J. R., Voci, G., and Cazals, F.: Pathophysiologic Study of the Lesser Circulation in the Course of Mitral Stenosis. Arch. mal. coeur **45:** 412 (May), 1952.

Clinical, electrocardiographic and roentgenologic findings in 50 cases of mitral stenosis were correlated with data obtained during cardiac catheterization. The latter included recordings of pulmonary capillary pressures, calculations of cardiac output, of pulmonary resistance, and of the size of the mitral valve ostium according to the formula of Gorlin.

Cardiac output in mitral stenosis is always lowered, but to a variable degree; the peripheral arterial oxygen saturation is normal or subnormal. An increase of the mean pulmonary pressure was found to be in direct proportion to the degree of pulmonary resistance. Pulmonary capillary pressure curves have a typical contour and diagnostic alterations were seen in the presence of mitral regurgitation. If the calculated mitral valve surface exceeds 2 sq. cm. no pathophysiologic signs of mitral stenosis can be demonstrated. A rumbling diastolic apical murmur, enlargement of the right heart and right ventricular strain in the electrocardiogram develop with diminution of the valve size below 2 sq. cm. When the latter is less than 1.5 sq. cm. one has to deal with a disease of severe character. A low gradient between pulmonary arterial and capillary pressures is found in patients with tendency to pulmonary edema, while in patients with a high gradient the pulmonary capillary bed appears to be protected by the increase of resistance in the pulmonary arterioles.

Commissurotomy releases the obstacle at the mitral valve but does not acutely change pulmonary resistance developing over years. Hence, success or failure of the operation cannot be judged from comparative studies performed shortly after surgery but only on the basis of a long term evaluation of the patient. Indication for surgery should take in account the duration of the disturbed function, the age of the patient and repeated signs of aggravation of the condition Such an evaluation can be made on clinical, roentgenologic and electrocardiographic basis and does not require cardiac catheterization. The latter should be reserved for cases in which coexistent mitral insufficiency is suspected.

PICK

Gorlin, E., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the Circulatory Dynamics at Rest in Mitral Valvular Regurgitation with and without Stenosis. Am. Heart J. **43:** 357 (March), 1952.

The authors have analyzed the circulatory dynamics of mitral regurgitation with and without stenosis by means of hydraulic principles and the technic of cardiac catheterization. Recognizing the errors introduced by various assumptions and indirect measurements, the authors state that the values derived from the hydraulic formulas serve as estimates and not as precise calculations.

Twelve patients with mitral valvular regurgitation were studied, one had pure congenital mitral insufficiency and 11 had both regurgitation and stenosis. The mitral valve orifice areas were measured at autopsy or digitally at operation in six patients for a total of nine studies. In the patient with pure mitral insufficiency, the total left ventricular output was calculated to be 61 cc. per beat per square meter, of which 37 cc. was aortic and 24 regurgitant through the mitral valve. In the 11 patients with both regurgitation and stenosis, the average total left ventricular stroke output was 57 cc., of which 26 was aortic and 31 cc. regurgitant. Thus regurgitant blood flow constituted one-half of the total ventricular discharge. Left ventricular pressure work and pulmonary "capillary" pressure and pulmonary arteriolar resistance were increased. Right ventricular pressure work on the average was within normal limits, and right ventricular failure was not common (three cases). Mitral stenosis tends to restrict available left ventricular stroke volume and to elevate pulmonary pressures, while mitral insufficiency tends to limit the aortic output for a given degree of stenosis. The regulation of aortic blood flow in the presence of mitral insufficiency depended on (a) the left ventricular volume and stroke capacity, (b) the degree of mitral regurgitation and the degree of mitral stenosis, (c) the height of the total pulmonary resistance, (d) the presence of aortic stenosis and the level of systemic vascular resistance, and (e) myocardial incompetence.

The authors stress the difficulty in making the differential diagnosis clinically between pure mitral stenosis and mitral insufficiency in association with stenosis. Easy fatigability was the most common and prominent complaint, and usually overshadowed the moderate degree of dyspnea present. A loud apical systolic murmur was consistent but not diagnostic of mitral regurgitation.

HELLERSTEIN

Ellis, L. B., Mebane, J. G., Maresh, G., Hultgren, H. N., and Bloomfield, R. A.: The Effect of Myxedema on the Cardiovascular System. Am. Heart J. **43:** 341 (March), 1952.

This is a study of the hemodynamics of the circulation of five patients with myxedema, including observations during exercise in two and studies made after medication with thyroid extract in two.

Cardiac outputs were determined by the direct Fick method. There was no uniformity in the response of the cardiovascular system to myxedema, although certain changes occurred in all cases: diminished cardiac output, reduced circulating blood volume, increased peripheral resistance in the systemic circulation and normal intracardiac pressures. In three cases, the cardiac output was reduced in proportion to the reduction in oxygen consumption. The peripheral utilization of oxygen remained within normal limits. In two patients, the reduction of cardiac output was out of proportion to the decrease in oxygen consumption. The absolute levels were of the order seen usually in severe heart failure or shock. One of the two patients had symptoms of cardiac insufficiency and the other had angina of effort. The latter patient developed an elevation of the pulmonary artery and ventricular diastolic pressures during exercise His angina had first occurred under thyroid medication and disappeared when this was stopped; it reappeared at a later date while he was severely myxedematous, again diminishing under renewed thyroid therapy.

The authors point out that the variety of circulatory patterns in the myxedematous state are due to the combined effects of myxedema itself and possibly associated atherosclerosis.

HELLERSTEIN

Morse, M., Schlutz, F. W., and Cassels, D. E.: The Lung Volume and Its Subdivisions in Normal Boys 10–17 Years of Age. J. Clin. Investigation **31:** 380 (April), 1952.

The inspiratory capacity and the expiratory reserve volume and residual lung volume in the resting recumbent state were determined by spirometric methods in 124 normal healthy boys ranging in age from 10 to 17 years The total lung capacity, vital capacity, and functional residual capacity were calculated. In order to determine the effects of various physical characteristics of these volumes, the results were statistically analyzed. It was found that height, or height^3, is the best single standard of reference, but increased accuracy is gained by multiple regression equations including one or two standards of reference in addition to height^3. Preference was given to the index of build or chest girth and the index of fat rather than to actual or normal weight or age.

In the resting recumbent position, the relative proportions of the total lung capacity occupied by the inspiratory capacity and the expiratory reserve and residual volumes were found to be 63.9, 17.0, and 19.1 per cent, respectively, in the boys of this group. Relatively lower values for the expiratory reserve and residual volumes at age 13 and 15 were noted. The indication that boys of 13, 14, and 15 years of age tend to have smaller lung volumes for a given height^3, chest girth, and index of fat also raises the question of nonlinearity of trend with age.

WAIFE

Brecher, G. A.: Mechanism of Venous Flow Under Different Degrees of Aspiration. Am. J. Physiol. **169:** 423 (May), 1952.

Changes in intrathoracic pressure were represented by direct aspiration of the peripheral end of the divided superior vena cava in dogs. At first there was a continuous reduction of the filling state of the vein. During this time outflow from the vein increased in proportion to the pressure gradient with an unchanged resistance. Later when the veins were less filled outflow was constant and resistance increased as pressure gradients went up. It is pointed out that in the first stage the extrathoracic veins empty part of their contents into thoracic veins. This will increase venous return during inspiration. When the veins are collapsed in very deep inspiration there is no further flow increase.

OPPENHEIMER

McInally, M., Campbell, J. A., Robertson, D. J., and Douglas, D. M.: The Clearance of Radiosodium from the Subcutaneous Tissues of the Leg. Clin. Sci. **11:** 183 (May), 1952.

The authors determined the rates of clearance of radiosodium from the subcutaneous tissues of the legs in normal subjects under various conditions, and in a group of patients with vascular disease. The clearance rates were found to be exponential, and there was some variation in normal subjects under the same conditions. As a rule fast clearance in one leg was accompanied by a fast rate in the other leg of normal persons. In unilateral disease, the unaffected leg might be used as a control. Clearance rates were usually increased by reflex vasodilatation, decreased by venous occlusion, and brought to a stop by arterial occlusion. The authors conclude that the clearance rate is largely governed by the amount of blood flowing through a part.

ENSELBERG

PATHOLOGY

Taylor, J. D.: Post-mortem Diagnosis of Air Embolism by Radiography. Brit. M. J. **4764:** 890 (April), 1952.

It would appear that radiologic examinations carried out within a short period of death are a most satisfactory means of diagnosis. The presence of air in the blood vessels and in the heart cavities can be seen with certainty. This procedure was followed in two cases of air embolism reported. Regional radiologic examinations were made on the cadavers within an hour of death. It is unlikely that air detected by radiologic means within an hour of death could be accounted for by the presence of gas-producing organisms in the two cases studied.

A case of arterial air embolism and one of pulmonary air embolism were discussed. In each case necropsy was preceded by regional radiographic examinations of the cadavers. The results of these examinations are reported. It was shown that radiologic examinations are a useful adjunct to the actual diagnosis, and also proved a guide to the most advantageous method of dissection to be followed in each case.

BERNSTEIN

Espino Vela, J., Velasquez, T., and Fuenmayor, A.: Aortoventricular Shunt Through the Right Coronary Artery. Arch. Inst. cardiol. Mexico **21:** 686 (Dec. 31), 1951.

A 13 year old patient with loud systolic and diastolic murmurs died of bacterial endocarditis. Autopsy disclosed an anomalous right coronary artery emptying into the right ventricle and causing a left to right shunt. The bacterial vegetations were chiefly developed in this anomalous artery.

LUISADA

Rubin, I. L., and Buchberg, A. S.: The Heart in Progressive Muscular Dystrophy. Am. Heart J. **43:** 161 (Feb.), 1952.

The authors have studied a series of 33 patients with progressive muscular dystrophy. In 6 of 12 postmortem examinations, lesions in the cardiac muscle were identical with those in the skeletal muscles. Electrocardiograms were available in 17 patients. In five, the P-R intervals were short, 0.10 to 0.11 second. In two patients, abnormal Q waves were present, probably due to the destruction and replacement of normal myocardial fibers by some process similar to that involving peripheral muscles. Clinically the majority of the patients showed no heart disease. If a sufficient amount of cardiac muscle is involved, congestive heart failure develops and responds to the usual methods of therapy.

HELLERSTEIN

Woods, F. M., and Kenney, L. J.: Congenital Aortic Aneurysm. J. A. M. A. **148:** 1216 (April 5), 1952.

A routine survey chest roentgenogram disclosed an abnormal shadow in the upper mediastinum of a 15 year old school girl. Physical findings were not diagnostic, but since a tumor could not be ruled out, surgical exploration was advised. Aneurysmal dilatation of the side of the aorta involving the first part of the descending portion just below the arch was found. Its upper limit lay just inferior to the origin of the left subclavian artery. Because the lesion was alarmingly thin-walled and pulsated slightly with a definite palpable bruit, it was felt that excision would have been ideal, but it was doubtful that the lesion could be completely resected, and the dangers of this technic would have been great. The method chosen for surgical treatment was simple in that the sac was infolded and tamponaded against the approximated edges of the defect. The patient's postoperative course was uneventful for 17 months. She has gradually re-

sumed normal activities; there have been no untoward effects and no evidence of recurrence on roentgenograms.

KITCHELL

Blum, J. E.: The Problem of Cardiac Polyps. Cardiologia **20:** 193 (Fasc. 4), 1952.

The author presents five instances of polypous intracardiac tumors found at autopsy. Histologic studies revealed that from the pathogenetic standpoint and according to their microscopic structure, two main groups can be distinguished. One represents myxomatous transformation of organized cardiac thrombi which can be attributed to penetration of edema fluid into the organizing connective tissue. Theoretically it can be assumed that a similar mechanism operates in the formation of true cardiac myxomata. Another type of tumor, usually carrying long tapering tentacles, termed by the author "benign papillary endothelial polyp," is a true endothelial new growth, which, on the basis of its histologic patterns can be differentiated from an organized myxomatous thrombus as well as from a true myxoma.

PICK

PHARMACOLOGY

Tyrer, J. H.: The Peripheral Action of Digoxin on Venous Pressure: A Study Using Sheep with an "Artificial Heart". Med. J. Australia **1:** 502, (April), 1952.

A double perfusion pump capable of maintaining, at constant or varying rates, the pulmonary and systemic circulations of anesthetized sheep is described. In each of four sheep whose hearts had been replaced functionally by the double perfusion pump which perfused the pulmonary and systemic circulations at constant rates, addition of Digoxin to the systemic venous reservoir was followed by a rise of pressure in the inferior vena cava.

The cause of the rise of pressure in the lower part of the inferior vena cava would seem to be one or other of the following: (a) a slight general venoconstriction along the length of the inferior vena cava, increasing slightly the gradient of pressure fall along this portion of the venous system from the periphery; (b) a more localized sphincter-like venoconstriction of the upper part of the inferior vena cava; (c) a theoretic possibility, considered unlikely but not as yet excluded, that while total vena cava blood flow was known to be constant, Digoxin might have selectively caused a diminished blood flow along the superior vena cava and an increased blood flow along the inferior vena cava, the latter producing the increase in inferior vena cava pressure.

Digoxin has a direct peripheral action, increasing the gradient of pressure fall along the inferior vena cava, apart, of course, from any direct action on the myocardium. The fact that in any case a peripheral action of Digoxin on venous pressure can be demonstrated does not suggest that the principal action of Digoxin in intact sheep is on venous pressure; in the control sheep with intact circulations, continuous records of mean right auricular pressure for one to one and a half hours after the intravenous injection of Digoxin showed no significant change in three sheep, and a fall in pressure of 2 cm. saline in one sheep.

BERNSTEIN

Ludwig, B. J., Holfeld, W. T., and Berger, F. M.: Cation Exchange Properties of Alginic Acid. Proc. Soc. Exper. Biol. & Med. **79:** 176 (Jan.), 1952.

This report deals with the results of in vitro experiments conducted to determine the cation adsorbing capacity and ion selectivity of alginic acid. Alginic acid is obtained from the giant kelp (*Macrocystis pyrifera*). It is a polymeric anhydro-B-D-mannuronic acid, chemically related to cellulose and pectic acid. Alginic acid possesses one carboxy group for each anhydromannuronic acid residue, and this free carboxy group is responsible for its ability to form water soluble gels with alkali metal ions. Alginic acid possesses sodium and potassium ion exchange properties which compare favorably with those of a carboxylic type cationic exchange resin (Natrinil). Under in vitro conditions, alginic acid at pH 7.6 adsorbs 4.2 mEq. of sodium ion per gram. The total cation adsorption from solutions containing potassium and sodium ions is also 4.2 mEq. per gram, and the ratio of sodium to nitrogen combined approximates that present in solution. The adsorption of calcium ion by alginic acid is irreversible and independent of the pH. The hydrophilic character of the sodium and potassium alginates may contribute to the elimination of fluid and cause laxation.

MINTZ

Fukuda, T., and Kushizaki, K.: The Cardiac Reflex as the Cause of Digitalis Emesis. Kyushu Mem. M. Sc. **2:** 137 (Dec.), 1951.

To evoke emesis, g-strophanthin was given to the dog intravenously. It was concluded that digitalis-emesis is caused by the centripetal impulse from the heart, because it is abolished completely after dissection of the centripetal cardiac fibers contained in the first and third groups of cardiac nerves. The impulse is conducted chiefly along the vagosympathetic fibers at the neck, but partly through the stellate ganglia to the center. The reflex from the abdominal organs inclusive of the liver cannot be wholly excluded as a cause of digitalis-emesis, but its role seems to be very small. The aortic and the carotid sinus reflex have no role in digitalis vomiting.

BERNSTEIN

King, B. D., Sokoloff, L., and Wechsler, R. L.: The Effects of l-Epinephrine and l-Nor-epinephrine

upon Cerebral Circulation and Metabolism in Man. J. Clin. Investigation **31:** 273 (March), 1952.

Cerebral hemodynamics were studied following continuous intravenous infusions of synthetic l-epinephrine and l-norepinephrine in man. Epinephrine produced an increase in mean arterial blood pressure and cerebral blood flow without a change in cerebrovascular resistance. The cerebral oxygen consumption increased significantly. On the other hand, norepinephrine produced a marked increase in cerebrovascular resistance with a decrease in cerebral blood flow. Cerebral oxygen consumption was not significantly altered by this compound. If the vascular beds of other organs, such as heart, liver, and kidneys, respond with vasoconstriction, as do the vessels of the brain, therapy with this and similar acting drugs might be unsatisfactory or actually harmful under certain clinical conditions. Norepinephrine and related drugs should be evaluated, not only by measurement of their pressor effects, but also by study of their blood flow to vital organs in normotensive and hypotensive states.

WAIFE

Kutz Echave, R.: Angina Pectoris. Pathogenetic Concepts and Sympathicolytic Treatment. Cardiologia **20:** 129 (Fasc. 3), 1952.

Twelve patients suffering typical angina pectoris, with and without evidence of myocardial infarction, were treated with Hydrergin, 10 to 20 drops three times daily over a period of several weeks to months. The anginal pain disappeared in nine cases and improved in one; in two instances the drug had no effect. Clinical improvement was not always associated with improvement of the electrocardiographic findings. The tracings became normal in two, less abnormal in four patients, and did not change in six.

The results are discussed with reference to data in the literature concerning sympatholytic effects of ergot alkaloids, the role of Adrenalin in the regulation of coronary circulation, and its direct effect on the metabolism of the myocardium.

PICK

Moyer, J. H., Miller, S. I., Tashnek, A. B., and Bowman, R.: The Effect of Theophylline with Ethylenediamine (Aminophylline) on Cerebral Hemodynamics in the Presence of Cardiac Failure with and without Cheyne-Stokes Respiration. J. Clin. Investigation **31:** 267 (March), 1952.

Cerebral hemodynamics were studied in 16 patients in cardiac failure, four of whom had Cheyne-Stokes respiration. It was found that after 0.5 Gm. of aminophylline in 10 ml. of saline intravenously in a five-minute period, the cerebrovascular resistance increased. As a result, the cerebral blood flow decreased. Evidence has been presented to show that this effect is a direct one on the cerebral vessels. The cerebral oxygen consumption appears to decrease after the administration of aminophylline. No difference in the over-all hemodynamic picture was noted in patients with Cheyne-Stokes respiration and those with regular respiration. The arrest of Cheyne-Stokes respiration after aminophylline cannot be attributed to an increase in cerebral blood flow. Probably it is due to a stimulating effect on the respiratory center. This may be due to a direct effect on the center or an indirect one by increasing the medullary carbon-dioxide resulting from circulatory stasis.

WAIFE

Imig, C. J., Randall, B. F., and Hines, H. M.: Effects of Epinephrine and Nor-epinephrine on Blood Flow Through Normal and Denervated Limbs of Dogs. Am. J. Physiol. **169:** 22 (April), 1952.

In doses which do not change blood pressure, both epinephrine and norepinephrine increased femoral arterial blood flow in normal and denervated limbs. Smaller doses of both drugs were required to increase blood flow in denervated limbs than in normal ones.

OPPENHEIMER

Prentice, T. C., Berlin, N. I., and Lawrence, J. H.: Effect of Therapy on Blood Volume, Blood Pressure, and Spleen Size in Polycythemia Vera. Arch. Int. Med. **89:** 584 (April), 1952.

Serial blood volumes were determined in 20 patients with polycythemia vera. During the fall in blood volume following therapy, two patterns were predominant: (1) a fall in total blood volume and (2) a fall in total red cell volume and a rise in plasma volume, with resulting fall in total blood volume. The factors which control plasma volume under these conditions are not known. The frequency of pattern 1 and of pattern 2 is about equal.

No simple or constant relationship could be noted between blood volume changes and rise or fall in blood pressure. This was true for both hypertensive and normotensive patients. The size of the spleen decreased rapidly and to a marked degree after therapy in all but one of the patients in whom the organ was originally palpable, and remained smaller for varying periods. The changes in spleen size did not appear to be a direct or simple function of blood volume. One cannot accurately judge changes in blood volume in polycythemia vera by red blood cell count or hematocrit. Both varied oppositely from the total blood volume in 34 per cent of instances.

BERNSTEIN

Werko, L., Bucht, H., Josephson, B., and Ek, J.: The Effect of Nor-adrenalin and Adrenalin on Renal Hemodynamics and Renal Function in Man. Scandinavian J. Clin. Lab. Investigation **3**. 255, 1951.

Pure Adrenalin and noradrenaline were found to depress the renal plasma flow, noradrenaline more than Adrenalin. Decreases of up to 50 per cent or more were observed. The total renal resistance increased. These preparations had no influence on the renal extraction of para-aminohippuric acid (PAH) studied by means of renal-vein catheterization. No influence on the diuresis could be observed. The inulin clearances showed only small changes in both directions, so that the filtration fraction (FF) was always increased. The renal arteriovenous oxygen difference remained constant after noradrenaline, but increased slightly after Adrenalin.

BERNSTEIN

Lands, A. M.: The Cardiovascular Actions of 1-(Aminophenyl)-2-aminoethanol and Related Compounds. J. Pharmacol. & Exper. Therap. **104:** 474 (April), 1952.

Studies of the pressor action, bronchodilator action and acute toxicity of four synthetic analogs of 1-phenyl-2-aminoethanol, in which an m-amino group was introduced into the ring, are reported. 1-(3-aminophenyl)-2-aminoethanol and the corresponding -2-methylamino and -2-ethylamino analogs were found to be effective vasopressor agents in anesthetized dogs; 1-(3-aminophenyl)-2-isopropylaminoethanol had a depressor action. Neither the latter compound nor the primary amine, 1-(3-aminophenyl)-2-aminoethanol, were effective in preventing bronchoconstriction in guinea pigs exposed to a histamine aerosol. The acute toxicity, as determined by intraperitoneal and intravenous injection in albino mice, appeared to be less than that of the corresponding unsubstituted and m-hydroxy analogs.

SAGALL

Sherrod, T. R.: Strophanthin-G on Coronary Sinus Outflow. J. Pharmacol. & Exper. Therap. **104:** 445 (April), 1952.

The effect of intravenous infusion of strophanthin-G on the coronary sinus outflow of the heart "in situ" was studied by means of a metal cannula inserted into the coronary sinus of anesthetized dogs. Doses of 3 micrograms per kilogram of body weight at five-minute intervals produced first a moderate decrease in the coronary sinus outflow. This was followed by a marked and sustained increase in flow. These changes occurred in the absence of significant changes in blood pressure or heart rate.

SAGALL

PHYSIOLOGY

Cerletti, A. and Weissel, W.: The Question of Electromechanic and Electropressoric Latency and of the So-called Time of Isometric Contraction of the Heart. Ztschr. Kreislaufforsch. **41:** 242 (April), 1952.

In order to study the exact time relationship of mechanical, acoustic, and electric events during the cardiac cycle, simultaneous recordings were made in 12 anesthetized dogs of pressure and volume curves of the left and right ventricle, pressure curves of the aorta, the phonocardiogram, and the electrocardiogram. The time interval between onset of QRS in the electrocardiogram and the beginning of pressure elevation in the left ventricle varied between 30 and 50 seconds per 1000. This time interval, termed by the authors the "electropressoric latency," was considerably greater than the "electromechanical latency" defined by the interval between onset of QRS and beginning of the volume curve of the ventricle, which measured only 10 to 15 seconds per 1000. Thus the so-called "time of isometric contraction," usually determined by correlation of electrocardiogram, heart sounds, and central sphygmogram, is actually a complex consisting of the true time of isometric contraction plus electropressoric as well as electromechanical latency. The time difference between the two latter values is apparently spent for transformation of the heart from its ovoid diastolic form into a more spheroid presystolic one.

PICK

Hensel, H.: A New Method for Recording of the Peripheral Circulation. Ztschr. Kreislaufforsch. **41:** 251 (April), 1952.

The author describes a new device for continuous registration and quantitation of peripheral arterial circulation which can be used for any place of the body surface. The method is based on calorimetric principles, and it is claimed that it avoids the usual errors involved in measurements of the skin temperature. A small chamber, the bottom of which is a thin silver plate and through which water circulates at a constant speed and temperature, is placed on the area of the skin to be examined. Differences of the temperature of inflowing and outflowing water are determined continuously with the help of thermobattery. Variations of peripheral circulation leading to alterations of the skin temperature can thus be determined with an accuracy of ± 0.0002 calories per second per square centimeter. Examples of recordings of acute changes of peripheral arterialization under various conditions are presented.

PICK

Sikand, R. S., Nahum, L. H., Levine, H., and Geller, H.: Ventricular Excitability of the Intact Dog Heart. Yale J. Biol. & Med. **24:** 366 (April), 1952.

The authors devised a method of delivering timed stimuli through a needle electrode inserted into the intact animal heart. They found that the diastolic threshold fell as anesthesia lightened, and vice versa; the threshold rose as heart rate increased; and in general, the threshold was lowest at the

apical region and highest at the basal region of the ventricles.

The total refractory period did not correspond to the Q-T interval, and its duration depended upon the shape of the precordial T wave. At the apex the total refractory period was shorter than at the base, provided the precordial T wave was upright. However, when the precordial T wave was negative, these findings were reversed. The implication from these findings is that recovery at the apical region is faster than at the base when the T wave is upright, and vice versa. So far as Q-T measurements are concerned, the authors point out that the Q-T interval does not truly represent the period of excitation and recovery of the ventricles, and that the total refractory period does not end at a specific point at or beyond T but varies in different regions of the heart. The usual clinical methods of estimating Q-T duration tend to produce too short a value. The precordial electrocardiogram is best suited to the measurement of the Q-T interval if only one lead is to be used.

ENSELBERG

Edelman, I. S., Olney, J. M., James, A. H., Brooks, L., and Moore, F. D.: Body Composition: Studies in Human Being by the Dilution Principle. Science **115:** 447 (April 25), 1952.

This is a review of the history, general principles, and recent advances in the study of the composition of the human body by means of the dilution of various substances, some of which may be traced by radioactive tracer technics. According to the authors, there is no perfect plasma-volume determination technic. For example, since there are large amounts of albumin outside the plasma in the lymph of liver and viscera, any valid albumin tracer will equilibrate into these areas outside the plasma. Radioactive iron-tagged red cell methods seem to be the best. Other isotopic red cell tags (P^{32}, Cr^{51}) show variable rates of leakage of the tags because they are held in the cell by a binding less stable than that of iron and hemoglobin. Furthermore, there are truly more red cells per unit of blood in large vessels than in the body as a whole. Normal blood volume varies from 7 to 9 per cent of body weight in healthy young adult males, and from 6 to 8 per cent in young adult females.

All the methods for the measurement of extracellular fluid involve technical difficulty and interpretive uncertainties because no substance has yet been identified that is a small molecule readily diffusible into all extracellular areas, nonmetabolized and exclusively extracellular in distribution.

Deuterium has been used to measure total body water. It appears that when plasma volume and transcellular water (the latter term being extracellular water and fluid in the cerebral spinal fluid, gastrointestinal tract, bile, etc.) are subtracted, an interstitial fluid in the general neighborhood of 12 to 15 per cent of body weight is obtained.

The total body water in normal males is 62 per cent of body weight and in the female 51.5 per cent. This includes plasma water, red cell water, interstitial water, all the varieties of lymph, and all the intracellular and transcellular water.

Measurements of sodium and potassium ordinarily do not include areas of slow or incomplete exchange (for example red cells for potassium, bone for sodium). Therefore, using total "exchangeable" sodium and potassium measurements, it appears that the mean exchangeable sodium in young adult males is 41.4 mEq. per kilogram.; in females, 41.0. The mean exchangeable potassium in young adult males is 46.8 mEq. per kilogram; in females, 40.7.

Interesting data relative to rates of exchange and metabolic correlations with total body fat are also included. The metabolic response to surgery is characterized chiefly by oxidation of fat, degradation of protein, loss of potassium, transfer of sodium into cell, and a tendency to increase body water.

WAIFE

RHEUMATIC FEVER

Kirschner, L., and Howie, J. B.: Rheumatic-like Lesions in the Heart of the Rabbit Experimentally Induced by Repeated Inoculation with Hemolytic Streptococci. J. Path. & Bact. **64:** 367 (April), 1952.

Pathologic changes are described in the hearts of rabbits subjected experimentally to focal streptococcal infections. The lesions were found especially in the myocardium, valves, endocardium and coronary vessels. There was intensive infiltration of the connective tissue between the muscle fibers (Aschoff-like nodules) and marked collagen degeneration. Marked changes in the antistreptolysin titer were observed. These histologic and serologic changes are closely similar to those seen in rheumatic fever.

BERNSTEIN

Lewy, F. J.: Diagnostic Problems of Rheumatic Fever and Their Impact on the Management of the Rheumatic Fever Patient. Ann. Int. Med. **36:** 1042 (April), 1952.

Only an integrated rheumatic fever community program based on close cooperation between clinics, hospitals, cardiologists, practicing physicians, school physicians, nursing, social, and educational services and vocational guidance can deal effectively with this long-term protean disease which is repetitive and often economically catastrophic. Early detection of this elusive disease is a primary objective, but in this connection experience has indicated that a staff of experienced and meticulous observers in a teaching hospital were unable to rule out or to confirm the presence of activity in 20 per cent of pa-

tients in whom rheumatic fever posed a problem. Experience with rheumatic fever programs has shown that communities may be alerted to the needs of obviously handicapped cardiac children but fail to provide a reasonable amount of supervision for questionable cases or for individuals with a history of rheumatic fever who show no evidence of cardiac involvement. In these latter cases, the role of the cardiologist as an educator of the community and of the parents is evident. Parents, nurses, and other community workers are impressed by the discrepancies of medical opinions resulting from lack of uniform criteria and standards of adequate care and particularly by conflicting recommendations for physical activities. Preventive measures and the judicious management of questionable cases require just as much attention as the care of advanced cases. To correct an erroneous diagnosis of heart disease based on an adventitious murmur and to insist on a normal and active life is as important as to make a differential diagnosis of a rare congenital cardiac anomaly. The interest must not be confined to the structure and function of the heart in cases of rheumatic fever. The social structure of the rheumatic family and of the community in which rheumatic fever patients live, must also be a prime consideration.

WENDKOS

Glynn, L. E., and Loewi, G.: Fibrinoid Necrosis in Rheumatic Fever. J. Path. & Bact. **64:** 329 (April), 1952.

Fibrinoid material in subcutaneous nodules from patients with clinically active fever has been examined histochemically. It differs from fibrin in its fibrillar structure as revealed by silver impregnation and by its resistance to tryptic digestion. It differs from collagen in its argyrophilia and in its intensely positive para-aminosalicylic acid reaction. It resembles collagen in being attacked by trypsin after denaturation by heat or urea. Removal of polysaccharide by pectinase or extraction with potassium salts results in the simultaneous loss of the para-aminosalicylic acid reaction and argyrophilia. The authors conclude that the fibrinoid change is brought about by the infiltration of collagen with a polysaccharide-rich material, possibly a glycoprotein.

BERNSTEIN

Kuschner, M., Ferrer, I., Harvey, R. M., and Wylie, R. H.: Rheumatic Carditis in Surgically Removed Auricular Appendages. Am. Heart J. **43:** 286 (Feb.), 1952.

The authors found evidence of rheumatic activity in the form of subendocardial Aschoff bodies, in 4 of 11 fragments of auricular appendage removed during mitral commissurotomy. The finding of morphologic evidence of rheumatic activity in patients who clinically were presumed to be inactive emphasizes the difficulty in establishing the clinical diagnosis.

HELLERSTEIN

Shetlar, M. R., Schmidt, H. L., Lincoln, R. B., DeVore, J. K., Bullock, J. A., and Hellbaum, A. A.: Response of the Serum Polysaccharide Fractions and Protein Fractions Following Cortisone Treatment of Patients with Rheumatic Fever. J. Lab. & Clin. Med. **39:** 372 (March), 1952.

The serum nonglucosamine polysaccharide, glucosamine polysaccharide, albumin polysaccharide, alpha polysaccharide, and serum heat coagulation values were found to be greatly elevated, while the albumin percentage and albumin-globulin ratios were lowered in patients with rheumatic fever prior to cortisone therapy. Following treatment with cortisone, subjective clinical improvement was promptly followed by decreases in the serum nonglucosamine, glucosamine polysaccharide, albumin polysaccharide, alpha globulin polysaccharide, and heat coagulation values, and by increases in albumin and in the albumin-globulin ratio. When there was recurrence of rheumatic fever after cessation of treatment, it was accompanied by a return of the serum factors to the original state.

It appears that the studies of the serum polysaccharide components, serum heat coagulation values, and albumin percentages may be valuable aids in the evaluation of rheumatic fever patients.

MINTZ

Hansen, A. E.: Importance of Early Diagnosis in Acute Rheumatic Fever. J. A. M. A. **148:** 1481 (April 26), 1952.

Although the fundamental cause of rheumatic fever remains obscure, progress is being made in conquering this disease. The significant observation that active rheumatic involvement may be "nipped in the bud" by early administration of corticotropin (ACTH) or cortisone places great responsibility on the practicing physician. The physician must emphasize the importance of adequate follow-ups for the child with rheumatic fever, and all patients including those who have been given corticotropin or cortisone must be put on a prophylactic regimen as soon as there are evidences that the initial activity of the infection has subsided. Thereby recurrences may be greatly lessened, the incidence of bed-confining illness may be diminished, and the number of "cardiac cripples" may thus be reduced.

KITCHELL

BOOK REVIEWS

Vascular Diseases in Clinical Practice, ed. 2. *Irving S. Wright, M.D.* Chicago, Year Book Publishers, 1952. 552 pages, 116 figures. $8.50.

In a recent address to the American Heart Association, Dr. Isaac Starr remarked that progress in research in peripheral vascular disease has been steady but never meteoric. In the second edition, Dr. Wright has successfully incorporated into his book, *Vascular Diseases in Clinical Practice*, the most pertinent of the steady clinical advances of the past four years. The book should be valuable to those for whom it was designed in clinical practice.

In the discussion on atherosclerosis, the problem of nutrition is well condensed from the recent vast literature on the subject. Although no definitive dietary regimen is suggested, the author points out that our knowledge of the subject does not yet warrant such a measure. Dr. Wright also points out that vasodilator drugs in the treatment of arteriosclerosis obliterans are of limited value and unless they have selective action on the affected limb, may actually be harmful. This is an important and previously under-stressed concept. The search for an "ideal" vasodilator in peripheral vascular disease has certainly not ended. One of the best parts of the book is the section on anticoagulant therapy. Any physician contemplating the use of such therapy can read this with profit, if for no other reason than to review the "indications for caution in use of anticoagulants." The author enjoys excellent therapeutic results from the use of Tromexan. As he points out, however, some observers consider it more difficult to control than Dicumarol. Some clinics use both drugs: Tromexan to attain the original change of prothrombin time because of its more rapid action and Dicumarol for the prolonged treatment of the patient. The book also includes a chapter on frostbite and immersion foot. This has become a problem of considerable dimensions in current military medical history, although recent advances in clothing have been of some prophylactic value. Recent experimentation has led to the belief that pure immersion foot is probably not an actual disease of the blood vessels themselves. Finally, the reviewer would like particularly to commend the chapter entitled "Amputation: Psychologic and Physical Care." The importance of such care is only too well known to those of us who are interested in the problem of vascular disease.

ORVILLE HORWITZ

Spitzer's The Architecture of Normal and Malformed Hearts. *Maurice Lev, M.D., and Aloysius Vass, M.D. With a foreword by Otto Saphir, M.D.* Springfield, Ill., Charles C Thomas, 1951. 176 pages, 50 figures. $5.00.

Alexander Spitzer's "Über den Bauplan des normalen und missbildeten Herzens. Versuch einer phylogenetischen Theorie" was published in Virchow's Archives of Pathologic Anatomy in 1923, but the theory was not generally accepted and not widely read until Maude Abbott, followed by Taussig, Gibson, Blalock, Gross, Potts, Cournand, Bing and others, felt it necessary to have an understanding of a workable broad concept of the formation of the heart and of the malformations encountered at the autopsy table in order to diagnose and cure such abnormalities. Otto Saphir deserves great thanks for stimulating his associates, Maurice Lev and Aloysius Vass to translate this difficult, cumbersome German article which is replete with lengthy idiomatic and picturesque expressions. The translation is excellent and very readily understood.

Spitzer's article is written in two parts. The first part gives in detail the phylogenetic theory of the normal septation process. The second part is an extension of the phylogenetic theory applied to the malformations of the heart. The text of the article is well illustrated by 26 drawings without which the complex theory of septation and rotation would not be understandable. Lev and Vass have added a third part to this splendid volume, giving a summary of Spitzer's later article written in 1938. A criticism of Spitzer's theory is intelligently offered and an adequate modification of Spitzer's theory is presented by Lev and Saphir. Thus, we have in one volume Spitzer's original article, his final summarization of the phylogenetic theory, a criticism of the theory and Lev and Saphir's modification which makes the theory acceptable to students of the "Fundamental Law of Biogenesis."

To all students interested in cardiovascular problems this book is a "must" without reservations.

GEORGE C. GRIFFITH

Factors Regulating Blood Pressure. Transactions of the Fifth Conference, Feb. 15–16, 1951. *Edited by Benjamin W. Zweifach and Ephraim Shorr.* New York, Josiah Macy Jr., Foundation, 1951. 238 pages. $3.75.

This is the record of the last of a series of conferences relating to hypertension. The style is typical; however enjoyable or apropos the by-play may be during the session, it disturbs the reader's idea of the subject at hand; easy writing, still more, easy conversation, makes hard reading. For example,

the discussions of atherosclerosis by Drs. Barr, Kendall, Gofman and Sims are so completely interrupted that it is hard to discover their continuities. And then they are separated from the relevant discussions of Drs. Dock, Lansing, Katz and Wakerlin, by Dr. Goldblatt's paper on renal hypertension with its extensive discussion by Dr. Wakerlin, and by two interesting epidemiologic papers on cardiovascular disease in Denmark and Ceylon; the span of discontinuity ranges roughly "from Greenland's icy mountains to India's coral strands." Those familiar with the field will require the volume but will gain little from it; those who are not, will want original and better documented sources.

What of the accomplishment of the series? The sessions must have value to the participants or they would not go; these and others may find the record of I-told-you-so reference value, particularly this volume with its cumulative index. Those abroad who are deprived of opportunities for personal contact with the speakers probably find it very informing. Prompter publication in a more closely edited, less pretentious format might better serve the purpose. If the personal element of free discussion must be a matter of record, the technics of film and television have much to offer. But it is not and, in this style, cannot ever make up into a proper book.

A. C. CORCORAN

Correlative Cardiology: An Integration of Cardiac Function and the Management of Cardiac Disease. *Carl F. Shaffer and Don W. Chapman.* Philadelphia, Saunders, 1952. 525 pages. $9.50.

Despite the intriguing title and subtitle of this book, one finds here a trite rather than any fresh approach to cardiology. The book is intended for students. The handling of the material is superficial and the use of the outline form makes for dogmatism and lack of proper emphasis. For instance, from the description of the etiology of ventricular tachycardia, a student might well conclude that the arrhythmia occurs more often without apparent cause than as a complication of myocardial infarction. The book is poorly proportioned; one-tenth of the volume is devoted to physical diagnosis, and the description of the pulse is accorded as much space as the subject of body fluids and electrolyte balance. In some instances descriptions of technics and directions for the administration of drugs are inadequate. There is considerable repetition of minor details and unrevealing diagrams while much important matter is omitted. Yet these are minor faults in comparison with the lack of lucidity, the slipshod expression, the frequent self-contradiction and the surfeit of glaring errors that make this a bewildering and completely untrustworthy work.

From some passages, such as the discussions of the cardiac cycle (p. 24) and water and salt depletion (p. 44), and from many of the figures, this reviewer could extract no meaning whatsoever. Ofttimes the phrasing is so obscure as to require deciphering. For example, a figure which shows a nodal premature systole (p. 214) is titled "AV nodal premature systole (rhythm—if constant) without retrograde conduction (tachycardia—if rate increased) (nodal and ventricular escape)." Most of the definitions are loose and unprecise. Space limitations permit listing only a few of the numerous concepts and statements with which the reviewer disagrees. The authors imply that digitalis has little value in the treatment of congestive failure associated with sinus rhythm. They state that according to the backward failure theory, the primary event in the development of congestive failure is an increase in stroke volume and cardiac output (p. 254); that an S wave exceeding 5 mm. in any of the standard limb leads is abnormal (p. 165); that peripheral thromboses may occur during auricular or nodal tachycardia if the pulse pressure is very small (pp. 204, 217); that abdominal paracentesis may be indicated in the treatment of chronic left-sided failure (p. 262); that the palpitation noted with a premature beat is due to "the more forceful contraction after the pause" (p. 201).

There are scores of statements that the authors obviously could not have intended but which would nonetheless confuse and misinform the student. Again a few examples must suffice. Repeatedly there is confusion between left and right, systole and diastole, inspiration and expiration, millimeters, millivolts and centimeters, plus and minus, etc.; wrong numerals appear, and wrong words—"direction" instead of "duration" (p. 90), "injection" instead of "insertion" (p. 122), "RAO position" instead of "diaphragm" (p. 135). It is stated that with anterior myocardial infarction there is "late T inversion in lead 3" (p. 180); that the presystolic murmur of mitral stenosis is "frequently accompanied by a localized systolic thrill" (p. 300); that the subcutaneous nodules of rheumatic fever are "0.5 to 1.5 mm. in size" (p. 297); that the Valsalva maneuver consists of "inspiration with closure of the glottis" (p. 140); that the normal Q wave is "0.10 mm. in lead 1" and "to 0.2 mm. in V_4" (p. 165). There are such expressions as "the volume of the circulation delivered by the veins to the capillaries" (p. 111), "the junction of the left ventricle with the right cardiophrenic angle" (p. 140), and "hydrogen ion (pH) increase" (p. 31). The diagrams are no less confusing. One finds the aorta labeled as a pulmonary vein (p. 27), the left auricle labeled as right auricle (p. 136), and a heart with two right auricles (p. 119). The murmurs of interventricular septal defect (p. 278), patent ductus arteriosus (p. 281) and pulmonic stenosis (p. 286) are depicted as located to the right of the sternum. Diagrams supposedly illustrating that Q waves do not normally occur in lead V_1 repeatedly show Q waves in that lead (pp. 172 to 175). The figures on pp. 131 and 344 have arrows pointing in the wrong

direction. The formulas for mean unsaturation of capillary blood (p. 41) and for leads V_R and aV_R (p. 156) are wrong. The last formula on p. 124 is meaningless because the term "C" is not defined. The tables on pp. 109 and 110 list the circulation time as increased in anemia and shortened in polycythemia. The table on page 239 contains three columns (with some erroneous statements) not found in the article which is given as its source; and the table on page 240, which was incorrectly copied from the source cited, contains potentially dangerous misinformation.

A book so wanting in precision, clarity and accuracy cannot be recommended.

ARTHUR S. GLUSHIEN

Manual of Electrocardiography. *Benjamin F. Smith.* Houston, Elsevier Press, 1952. 215 pages, 119 illustrations. $4.50.

This is an excellent book for the senior medical student, the intern, the resident, and the general practitioner who has not had special training in this subject. It is definitely not for the advanced student of electrocardiography. The first three chapters are devoted to the electrocardiographic instrument, to cardiac anatomy and physiology of particular importance in electrocardiography, and to the theory of the production of an electric field by the heart beat. In chapters 4 and 5 electrocardiographic leads are thoroughly discussed as well as nomenclature of the tracing. Chapters 6 through 14 are devoted to diagnostic and clinical use of electrocardiograms. Chapter 15 is a rather unique one in that it is entitled "Correlation of Electrocardiographic and Autopsy Findings." The chapter would be improved by the addition of clinical findings and history in each case. Chapter 16 is entitled "Pen Pictures of Cardiology." It is quite interesting but has very little to do with electrocardiography. The volume does not deal with the newer concepts of spatial vector electrocardiography.

J. R. KITCHELL

Low-Sodium Diet. A Manual for the Patient. *Thurman B. Rice.* Philadelphia, Lea & Febiger, 1951. 103 pages, 14 food charts. $2.75.

In this brief book the author discusses the distribution of sodium in foods, drugs, and other ingestible substances. Suggestions for the preparation of low-sodium diets are given in some detail and useful lists of the sodium content of common foods are presented.

Except for perhaps over-emphasizing the significance of exogenous sodium, the book should prove helpful to patients and relatives who must be concerned with low-salt diets.

S. O. WAIFE

The Clinical Use of Fluid and Electrolyte. *John H. Bland, M.D.* Philadelphia, Saunders, 1952. 259 pages, 75 figures. $6.50.

The author is Assistant Professor of Medicine at the University of Vermont College of Medicine. His book contains 259 pages divided into 13 chapters. Four hundred and seventeen original references are included. The text is supplemented by 75 figures which demonstrate graphically the distribution of water and electrolytes between plasma, extracellular fluid and cells in the conditions discussed. The first chapter reviews normal fluid and electrolyte physiology. In the remainder are discussed the specific circumstances in which abnormalities may occur, including childhood, old age, surgery, cardiac and renal disease, diabetes, adrenocortical imbalance and the effects of various physical stresses. Each chapter opens with a detailed description of the relevant physiologic mechanisms, both normal and pathologic, which conforms closely to recent concepts. Treatment is then presented as a logical development from these considerations. The preclinical and clinical aspects of each condition are well integrated.

The book contains a large body of recent and detailed information, which has not hitherto been available in a single work. To be of greatest value, it should be studied, rather than read. Nevertheless, each chapter is sufficiently self-contained to be of immediate use to the clinician.

D. M. GREEN

Gli Elettroliti nella Funzione Contrattile del Miocardio e nella Genesi dell'Elettrocardiogramma (The Electrolytes in Myocardial Contraction and in the Origin of the Electrocardiogram). *F. Lenzi and A. Caniggia.* Siena, La Poligrafica, 1952. 355 pages, 93 figures, 11 graphs.

The ambitious theme of this monograph is developed through a series of electrocardiographic experiments plus a detailed review of the literature (over 1000 quotations). The experimental work is limited to one species (turtle), one method (electrocardiogram), and one lead, (unipolar, anterior, epicardial tracings). The investigation is based upon the result of systematic investigations with the various ions of Mendelejeff's series. The results are analyzed in detail but are poorly presented; most of them could be presented more clearly in tabular form. Correlation of the findings with the already known data is rendered confused by the excessive weight of quotations. No attempt at evaluation of the clinical importance of the findings is made.

While this book may be of some usefulness to workers in the same field, the purely analytic presentation strongly detracts from its value.

A. LUISADA

AMERICAN HEART ASSOCIATION, INC.

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ANNUAL MEETING SCHEDULE

Following is the daily schedule for the Association's Twenty-Ninth Annual Meeting and Twenty-Sixth Scientific Sessions to be held at the Hotel Chelsea, Atlantic City, N. J., Wednesday, April 8 through Sunday, April 12.

Wednesday, April 8

9:30 A.M.–5:00 P.M.: Assembly of the American Heart Association: Panel Discussions

Thursday, April 9

9:30 A.M.: Business Meeting of the Assembly, including Panel Reports.
1:00 P.M.: Assembly Luncheon, Address by Dr. Robert L. King, incoming President.
2:30 P.M.: Annual Meeting of Scientific Council.
2:30 P.M.: Session on Community Rheumatic Fever Programs, Staff Conference of Heart Associations, Assembly members and other guests invited.
7:00 P.M.: Annual Dinner Meeting of Council on Rheumatic Fever and Congenital Heart Disease.
7:30 P.M.: Special Scientific Session on Ballistocardiography and Vectorcardiography.

Friday, April 10

9:00 A.M.: First Regular Scientific Session, including a Panel on Prevention of Rheumatic Fever.
2:00 P.M.: Second Scientific Session, including the Lewis A. Conner Memorial Lecture by Dr. William Hamilton, Professor of Physiology, Medical College of Georgia.
7:30 P.M.: Annual Dinner of the American Heart Association, including presentation of Gold Heart Awards and Howard W. Blakeslee Award.

Saturday, April 11

9:00 A.M.: Third Scientific Session, including a Panel on Interruption of Sympathetic Pathways by Surgical and Medical Means.
2:00 P.M.: Fourth Scientific Session, including the George E. Brown Memorial Lecture by Dr. David P. Barr, Professor of Medicine, Cornell University Medical School, and Chief Physician at the New York Hospital.
7:30 P.M.: Annual Dinner Meeting of Section on Circulation.

Sunday, April 12

9:00 A.M.: Fifth Scientific Session, including a Panel on Surgery for Congenital Heart Defects.
2:00 P.M.: Sixth Scientific Session, including a Panel on Anticoagulant Therapy and a Clinical Pathological Conference.

STAFF CONFERENCE OF HEART ASSOCIATIONS

The annual meeting of the Staff Conference of Heart Associations, which is composed of executive directors and other staff members of heart associations, will be held in conjunction with the Annual Meeting of the American Heart Association, from Thursday, April 9 to Sunday, April 12, at the Hotel Chelsea, Atlantic City, N. J. A session on community rheumatic fever programs will be held on Thursday afternoon, April 9, and a discussion on employment and heart disease will take place on Friday morning, April 10. Members of the Assembly and Board and Committee members of heart associations are invited to attend these two sessions. The sessions are planned by the Staff Conference in cooperation with the national staff of the Association.

REPORTS ON CATHETERIZATION, ANGIOCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

The Committee on Catheterization and Angiocardiography of the Association's Scientific Council has prepared a report dealing with indications, contraindications, and possible complications related to these procedures.

The Council's Committee on Ballistic Terminology has issued its first report designed to achieve a uniform terminology for ballistocardiography. The report deals with basic definitions and nomenclature of displacement ballistocardiograms.

Both reports will be published in a future issue of CIRCULATION, and reprints will then be available.

André Cournand, M.D., New York City, is Chairman of the Committee on Catheterization and Angiocardiography. Members include: Richard J. Bing, M.D., Baltimore; Lewis Dex-

ter, M.D., Boston; Charles Dotter, M.D., New York City; Louis N. Katz, M.D., Chicago; and Earl Wood, M.D., Rochester, Minn.

Isaac Starr, M.D., Philadelphia, is Chairman of the Committee on Ballistic Terminology. Members include John R. Braunstein, M.D., Cincinnati; William Dock, M.D., Brooklyn, New York; Richard Gubner, M.D., New York City; W. F. Hamilton, M.D., Augusta, Ga.; John L. Nickerson, Ph.D., New York City; Maurice B. Rappaport, Cambridge, Mass.; William R. Scarborough, M.D., Baltimore; and John E. Smith, M.D., Washington, D. C.

SECTIONS ON CLINICAL CARDIOLOGY AND VASCULAR SURGERY

Officers and an Executive Committee have been named to serve on an interim basis during the organization of the New Section on Clinical Cardiology of the Scientific Council. The officers include: Chairman, A. Carlton Ernstene, M.D., Cleveland; Vice-Chairman, Emmet B. Bay, M.D., Chicago; and Secretary, Carter Smith, M.D., Atlanta, Ga. The Executive Committee includes: William G. Leaman, Jr., M.D., Philadelphia; Samuel A. Levine, M.D., Boston; John LaDue, M.D., New York City; Homer P. Rush, M.D., Portland, Ore.; Hugh J. Morgan, M.D., Nashville; and William Paul Thompson, M.D., Los Angeles.

George Humphreys, II, M.D., New York City has been named Chairman pro tem of the new Section on Vascular Surgery which is being formed. Dr. Jere W. Lord, Jr., New York City, has been appointed Secretary-Treasurer.

RHEUMATIC FEVER PROGRESS REPORT

The Council on Rheumatic Fever and Congenital Heart Disease has issued a progress report summarizing its accomplishments during the past two years. A copy of the report may be obtained by writing to the Association.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

The office of this Council in Cleveland has been closed as part of the process of integration within the framework of the American Heart Association. Functions relating to medical and program matters have been transferred to the national office of the Association in New York under the supervision of the Medical Director. The fund-raising activities of the Council will be conducted from the office of the Cleveland Area Heart Society.

The Council's Annual Spring Conference in Cleveland will be continued. The 1953 Conference will be held on May 15 and 16.

George E. Wakerlin, M.D., Chicago, Chairman of the Council's Medical Advisory Board, will serve as Chairman of the Program Committee of the May meeting. The Committee includes Caroline B. Thomas, M.D., Baltimore; Thomas Findley, M.D., New Orleans; Meyer Friedman, M.D., San Francisco; and Edward Weiss, M.D., Philadelphia.

PROCEEDINGS OF COUNCIL'S 1952 ANNUAL MEETING

The Proceedings of the 1952 Annual Meeting of the Council for High Blood Pressure Research have been published by the American Heart Association in a paper-covered monograph, which is available at $1.75 per copy. The Proceedings include six scientific papers and a number of informal addresses to the lay audience, presented at the Council's Annual Meeting last May, summarizing current developments in research and treatment in the cardiovascular field, including arteriosclerosis, coronary heart disease, hypertension, rheumatic heart disease, and congenital heart disorders. They include several original papers as well as reviews of recent original investigative work.

The scientific papers should be of special interest to investigators and to cardiologists, internists, and other practising physicians.

The reports to the laymen were made by physicians prominent in the activities of the American Heart Association, including clinicians as well as investigators. They were: Irving S. Wright, M.D., President of the American Heart Association; Louis N. Katz, M.D., Chairman of the Scientific Council; Robert W. Wilkins, former Chairman of the Medical Advisory Board of the Council for High Blood Pressure Research; Dr. Howard B. Sprague, Past President of the American Heart Association; and Dr. Irvine H. Page, a member of the Council's Medical Advisory Board.

The scientific papers include reports from widely scattered laboratories: Los Alamos Scientific Laboratory, New Mexico; the Research Division of the Cleveland Clinic Foundation; the National Heart Institute of the U.S. Public Health Service; the Medical Research Institute of the Michael Reese Hospital, Chicago; Yale University; and the Pathologic Institute, McGill University, Montreal.

DR. WHITE RECEIVES FIRST LASKER AWARD IN CARDIOVASCULAR FIELD

Paul Dudley White, M.D., Boston, has received the first annual Albert D. Lasker Award for distinguished achievement in the field of cardiovascular diseases. The award will be presented each year by the Albert and Mary Lasker Foundation through the American Heart Association. Dr. White's award was formally presented by Irving S. Wright, M.D., President of the Association, at the 1953 Heart Fund Dinner of the Massachusetts Heart Association. He received a prize of $1,000; a scroll describing his accomplishments; and a gold statuette of the Winged Victory of Samothrace, symbolizing victory over death and disease.

Internationally renowned as a cardiologist, teacher, and scholar, Dr. White was cited for his "remarkable insight and pioneering efforts in the pathology, diagnosis, and treatment of heart disease." He was a founder of the American Heart Association in 1922, and its President in 1940–41. Dr. White is Chairman of the Association's Committee on International Affairs, and will serve as President of the Second International Cardiological Congress to be held in the United States next year. He is Executive Director of the National Heart Advisory Council, and chief consultant to the National Heart Institute.

PROGRAM COMMITTEE

The Program Committee for the Annual Scientific Sessions includes the following:

Program Committee: André Cournand, Chairman, New York; Maurice Sokolow, Co-Chairman, San Francisco; Wright R. Adams, Chicago; Charles A. R. Connor, New York; Paul F. Dwan, Minneapolis; William F. Hamilton, Augusta; Fay A. LeFevre, Cleveland; Roy W. Scott, Cleveland; Carter Smith, Atlanta; John H. Talbott, Buffalo; Robert D. Taylor, Chicago.

Members of the Program Committees of the various Sections and Councils of the Scientific Council are as follows:

Council on Rheumatic Fever and Congenital Heart Disease: Paul F. Dwan, Chairman, Minneapolis; H. J. Dodge, Denver; Miss Eckka Gordon, New Haven; John P. Hubbard, Philadelphia; Miss Eleanor Mole, Brooklyn, N. Y.; David D. Rutstein, Boston; Helen B. Taussig, Baltimore; George M. Wheatley, New York.

Section on Circulation: Fay A. LeFevre, Chairman, Cleveland; Wilbur H. Duryee, New York; Hugh H. Hussey, Washington; Ernest W. Page, San Francisco; Simon Robard, Chicago; James V. Warren, Durham.

Section on High Blood Pressure Research: Robert D. Taylor, Chairman, Cleveland; Stanley Bradley, New York; Harold Green, Winston-Salem; Ernest W. Page, San Francisco; Arthur Scherbel, Cleveland.

Section on Clinical Cardiology: Wright R. Adams, Chairman, Chicago; Thomas J. Dry, Rochester; George C. Griffith, Pasadena; Calvin F. Kay, Philadelphia; Richard H. Lyons, Syracuse.

Section on Vascular Surgery: George H. Humphreys, II, Chairman, New York; Jere W. Lord, Jr., New York.

COMMUNITY SERVICE AND EDUCATION DIVISION

The Association's Board of Directors has approved the creation of a Council on Community Service and Education as a counterpart of the Scientific Council. The name of the Public Health Division of the Association has been changed to Community Service and Education Division to conform with this action. John W. Ferree, M.D., formerly Public Health Director, will now be known as Director of Community Service and Education. Functioning under his direction will be the staffs concerned with program consultation, public information, and educational materials.

Jerome H. Baker, formerly Educational Director of the Georgia Heart Association, has joined the national staff as a Field Program Consultant.

CHRONIC DISEASE PROCEEDINGS

The complete Proceedings of the Conference on Preventive Aspects of Chronic Disease held in Chicago on March 13–14, 1951, have recently been published. Copies may be obtained from the Health Publications Institute, Inc., Raleigh, N. C. The American Heart Association was one of the participating organizations in the Conference, which was sponsored by the Commission on Chronic Illness. The Association, with the National Heart Institute, drew up a Statement on Cardiovascular Diseases, which is included in the printed Proceedings.

TRIBUTE TO FRANK N. WILSON

A tribute to the late Frank N. Wilson has been received from the International Society of Cardiology through its Secretary-General, Dr. Pierre W. Duchosal. The statement reads:

"In 1950 the International Society of Cardiology nominated Frank N. Wilson, as honorary member, the first time such an honour was bestowed. This choice reflected a tacit testimony of cardiologists the world over for the work of this savant who was the genial constructor of modern electrocardiography.

"His death deprives the cardiology world of one of its most eminent pioneers.

"The Committee of the International Society of Cardiology in the name of its member Societies extends to Mrs. Frank N. Wilson its profound sympathy."

COURSE ON CONGENITAL AND RHEUMATIC HEART DISEASE

The Cook County Graduate School of Medicine announces a two-week intensive course on "The Diagnosis and Treatment of Congenital and of Rheumatic Heart Disease in Infants and Children," presented by Benjamin M. Gasul, M.D. and Egbert H. Fell, M.D., and associates, from May 18 to May 30. A circular giving full information may be obtained from the Registrar, Cook County Graduate School of Medicine, 707 South Wood Street, Chicago.

MEETINGS

Apr. 8–12: Twenty-Ninth Annual Meeting, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 8–9: Assembly panels, Assembly meeting, meeting of the Scientific Council, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Twenty-Sixth Scientific Sessions, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 13–17: American College of Physicians, 34th Annual Meeting, Hotel Chelsea, Atlantic City, N. J.

Apr. 20–22: Areal Meeting, American Academy of Pediatrics, Hotel Statler, Boston, Mass. Executive Secretary, E. H. Christopherson, M.D., American Academy of Pediatrics, 610 Church Street, Evanston, Ill.

Apr. 23–25: 1st Western Hemisphere Conference of World Medical Association, Richmond, Va. Secretary-General, Dr. Louis H. Bauer, World Medical Association, 2 East 103rd Street, New York 29.

May 3: National Meeting, American Federation for Clinical Research, Steel Pier, Atlantic City, N. J. Convention headquarters at Haddon Hall Hotel. National Secretary, Dr. Lawrence E. Hinkle, Jr., M.D., 525 E. 68th St., Room F-611, New York 21, N. Y.

May 7–10: National Congress of Cardiology, Sevilla, Spain. Secretary, Dr. E. Benot, 3 Paseo de las Delicias, Sevilla, Spain.

May 15–16: Annual Spring Meeting, Council for High Blood Pressure, Cleveland, Ohio.

CORRECTION: In the paper entitled "Intramural Depolarization Potentials in Myocardial Infarction: A Preliminary Report," by Prinzmetal, Kennamer, Shaw, Kimura, Lindgren and Goldman, published in the January 1953 issue of CIRCULATION, one statement requires correction. In the next to last sentence of the foreword, it is stated: "In the normal ventricle, positive depolarization potentials greatly predominate over negative potentials." This sentence should read: "In the normal ventricle, negative depolarization potentials greatly predominate over positive potentials."